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Original Research Paper

Carbamazepine solubility enhancement in tandem with swellable polymer osmotic pump tablet: A promising approach for extended delivery of poorly water-soluble drugs

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ABSTRACT

Elementary osmotic pump (EOP) is a unique extended release (ER) drug delivery system based on the principle of osmosis. It has the ability to minimize the amount of the drug, accumulation and fluctuation in drug level during chronic uses. Carbamazepine (CBZ), a poorly water-soluble antiepileptic drug, has serious side effects on overdoses and chronic uses. The aim of the present study was to design a new EOP tablet of CBZ containing a solubility enhancers and swellable polymer to reduce its side effects and enhance the patient compliance. Firstly, a combination of solubilizing carriers was selected to improve the dissolution of the slightly soluble drug. Then, designing the new EOP tablet and investigating the effect of different variables of core and coat formulations on drug release behavior by single parameter optimization and by Taguchi orthogonal design with analysis of variance (ANOVA), respectively. The results showed that CBZ solubility was successfully enhanced by a minimum amount of combined polyvinyl pyrrolidone (PVP K30) and sodium lauryl sulfate (SLS). The plasticizer amount and molecular weight (MW) together with the osmotic agent amount directly affect the release rate whereas the swellable polymer amount and viscosity together with the semi-permeable membrane (SPM) thickness inversely influence the release rate. In addition, the tendency of following zero order kinetics was mainly affected by the coat components rather than those of the core. Further,

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orifice size does not have any significant effect on the release behavior within the range of 0.1 mm to 0.8 mm. In this study we report the successful formulation of CBZ-EOP tablets, which were similar to the marketed product Tegretol CR 200 and able to satisfy the USP criterion limits and to deliver about 80% of CBZ at a rate of approximately zero order for up to 12 h.

1. Introduction

Oral delivery remains as the most preferable and convenient route of administration for majority of drugs. Although they provide a suitable balance of efficacy and safety with acceptable clinical performance [1], conventional immediate release (IR) dosage forms have severe adverse action due to dose fluctuation and more importantly, low patient compliance caused by frequent doses [2,3]. Therefore, the rationale for development of an ER formulation of a drug is to improve the patient compliance with prescribed dosing regimens, enhance the therapeutic effects, minimize the dose and hence the side effects [1].

The osmotic pump tablet (OPT) is distinguished by utilizing the osmotic pressure as energy source for drug release, and it represents one of the most promising technologies for ER delivery systems [4,5]. Thirty-one products have been developed and marketed based on osmotic technology and 161 patents were published on the formulation aspects of these systems until the year 2000. In addition to being potentially able to provide a constant release independently to the characteristics of the release medium [4], these devices possesses distinctive clinical benefits, such as minimizing the food-effect and the improvement of the treatment tolerability and patient compliance [6]. Various types of OPTs have been developed and studied to deliver drugs with different aqueous solubilities [7].

The convenience and simplicity to manufacture and evaluation, has contributed much to the popularity and commercialization of EOPs over other osmotic based systems [8]. They consist of a core, containing the active agent, an osmogent and other excipients, coated with SPM. One orifice is drilled in the SPM through which the drug is released after the generation of osmotic pressure by the osmogent when exposed to an aqueous environment [9]. EOPs are commonly used to deliver water-soluble drugs but recently, some researches had been carried out to enable the delivery of water-insoluble drugs by EOPs [10]. Various attempts were utilized, such as addition of a solubility modulating agent to the core formulations [11], crystal-habit modifying agents for drugs, like polymers, surfactants and/or wicking agents [12].

CBZ, a dibenzapine derivative, is widely used for the treatment of epilepsy to control different types of seizures. The drug absorption from IR dosage forms was slow and erratic [13] and at overdoses and chronic use, CBZ exerts serious side effects which signify the importance of its incorporation into ER system. It also presents a poor aqueous solubility which results into poor bioavailability after oral administration [14]. Many previously published researches have reported a successful improvement of CBZ solubility using solid dispersion technique [13,15–17]. However, the use of large amounts of polymer constitutes one of the major drawbacks due to difficulties in handling and formulation into a final dosage form especially for such high drug loading. Further, in solid dispersion, maintaining the physical stability of the drug and the vehicle still one of the major problems together with the preparation technique and the difficulty in up scaling [18].

Therefore, CBZ incorporation into an effective EOP delivery system along with its solubility enhancement would improve the bioavailability, reduce the side effects and avoid fluctuation in plasma level [19].

In the present study, the development of a new design EOP tablet for the poorly water-soluble drug (CBZ) by solubility enhancement and incorporation of swellable polymer into the core tablet, have been investigated and aimed to achieve an optimum USP limit, zero order release, once daily administration. Minimum amounts of a hydrophilic polymer (PVP K30) and surfactant (SLS) were combined by simple physical mixing and used as solubility promoter in order to prevent the agglomeration of drug particles and increase their wettability. Swellable polymer Hydroxypropyl methylcellulose (HPMC) that was used in core formulations helps in formation of uniform gel containing drug particles to be pushed out of the device after water imbibitions and acts as another driving force for drug release apart from osmotic pressure. The core and SPM components were optimized using single parameter analysis and Taguchi orthogonal array design (OAD), respectively, including the type and amount of osmotic agent, swellable polymer and plasticizer, SPM thickness and orifice size. The effect of these factors on the release rate and kinetics was discussed and the developed systems were statistically compared with marketed ER CBZ tablets.

2. Materials and methods

2.1. Materials

CBZ powder was purchased from Zhejiang Jiuzhou Pharmaceutical Co. Ltd. (Zhejiang, China). Cellulose acetate (CA, opadry CA 500F 190001) and HPMC (E5, K100LV and K100M) were from Shanghai Colorcon Coating Technology Ltd. (Shanghai, China). PVP K30 was from ISP. (Shanghai, China).

Mannitol was from Roquette Co. Ltd. (Shanghai, China). Fructose was from Shanghai Huixing Chemicals reagent Co. Ltd. (Shanghai, China). Potassium chloride (KCl) was from Shanghai Lingfeng Chemicals reagent Co. Ltd. (Shanghai, China). SLS was from Shanghai Sinopharm Chemical reagent Co. Ltd. (Shanghai, China). Polyethylene glycol (PEG) with MW of 400, 1000 and 2000 kDa was from Shanghai Xilong Chemicals reagent Co. Ltd. (Shanghai, China). Commercial ER tablets of CBZ (Tegretol CR 200 mg) were from Novartis Pharmaceuticals Ltd. (Italy). All other chemicals and solvents used were of analytical grade.

2.2. Methods

2.2.1. The CBZ solubilization by PVP K30 and SLS physical mixtures

Physical mixtures (PMs) of CBZ with PVP K30 alone or in combination with SLS were prepared in different ratios. The blending process was carried out with constant trituration to assure the uniform distribution of the drug among the additives. Subsequently, The resultant PMs were passed through 60-mesh sieve.

Solubility measurements of CBZ were performed as previously reported [20]. An excess amount (50 mg) of CBZ and PMs of respective ratios was added to 10 ml of aqueous solutions. The samples were sonicated for 1 h. Subsequently, they were shaken at 37 °C and 100 rpm for 48 h, filtered, suitably diluted and their absorbance was noted at 284 nm in a double beam UV/visible spectrophotometer (Rayleigh UV 9600, Beijing Ruili Analysis Equipment Co. Ltd., China).

2.2.2. Core tablets preparation and optimization

Single parameter optimization was used to study the influence of different core formulation variables on drug release. For the preparation of CBZ core tablets, all ingredients, including predetermined amount of CBZ-PM, were accurately weighed, passed through 60-mesh sieve, then well mixed by hand mixing and directly compressed into tablets on 12 mm concave punches under a pressure of 4–5 kg/cm^2, using TDP single Punch Tablet Press (Tianxiang Zhitai, Shanghai, China). The amount of microcrystalline cellulose, filler, was varied to fix each tablet weight at 660 mg (Table 1). After that, the core tablets were coated with CA (3% of weight gain) contained 40% of PEG 400, and the release behavior was examined and compared. The optimum formulation was selected to follow zero order kinetics and to satisfy the USP 29 specification limits for release rate from CBZ-ER tablet which were as follows; 3 h (10%–35%); 6 h (35%–65%); 12 h (65%–90%); 24 h (>75%).

Table 1 – The composition of CBZ core tablets.

Code	Osmotic agent (mg/each tablet)			Swellable polymer (mg/each tablet)		
	Mannitol	KCL	Fructose	E5	K100LV	K100M
F1	200				50	
F2		200			50	
F3			200		50	
F4	150				50	
F5	250				50	
F6	250			50		
F7	250					50
F8	250				25	
F9	250				75	

Each core tablet contained 200 mg CBZ and the fixed ratio of PVP K30 and SLS. The proper amount of magnesium stearate and talc were added also.

2.2.3. SPM preparation and optimization

Tablets were coated using spherical stainless steel pan coater (Huanghai Medicine & Drug Testing Instruments Technology Co. Ltd., Shanghai, China) with 3% (w/v) of CA dissolved in 90/10 (v/v) of acetone/water under the following conditions; pan rotating rate was 20 rpm; spray rate was 3 ml/min; drying was achieved by a heat gun and the coat thickness was calculated as the coating weight gain. Afterward, the coated tablets were incubated at 40 °C for 4 h in an oven to remove the residual coating solvent and to complete the film formation. Finally, one orifice was drilled on each coated tablet by laboratory laser drilling apparatus (Nanjing Rui Ma Electronic Engineering Technology Co. Ltd., China).

A Taguchi OAD L9 was used for coating formulation optimization. The four variables were selected as showed in Table 2. L and subscript 9 denote the Latin square and the number of the experimental runs, respectively. The run involved the corresponding combination of levels to which the factors in the experiment were set. All factors had three levels and the drug release rate at 3, 6, 12 and 24 h, and drug release kinetics were considered to be the responses variables. The optimum responses were selected to follow zero order kinetics and USP 29 specification limits described earlier.

2.2.4. In vitro release of CBZ from the prepared osmotic tablet

In vitro drug release studies were performed according to USP 29 specifications limits for CBZ-ER tablet, using the USP Type I dissolution test apparatus (ZRS-8G dissolution tester, Tianda Tianfa Technology Co. Ltd., China) at a basket speed of 100 rpm with 900 ml of water as drug release medium for 24 h at 37 ± 0.5 °C. 10 ml was withdrawn and replaced by the same amount of fresh medium at 1, 3, 6, 9, 12 and 24 h. Samples were filtered, suitably diluted and the absorbance was measured at 284 nm. A comparative evaluation has been done also with commercial ER tablets of CBZ (Tegretol CR 200). Drug release profiles were drawn using MS-Excel software.

2.2.5. Release kinetics and statistical analysis

The data was treated with zero order, first order and Higuchi equations (Eqs. (1), (2) and (3)) respectively [21].

Table 2 – Factors and levels for OAD L9.

Factors	Levels		
	1: low	2: medium	3: high
A: Plasticizer type	PEG400	PEG1000	PEG2000
B: Plasticizer amount (% CA)	20	40	60
C: SPM thickness (% weight gain)	3	5	7
D: Orifice size (mm)	0.1	0.4	0.8

$$Q_t = K_0 t \quad (1)$$

$$\ln Q_t = \ln Q_0 - K_1 t \quad (2)$$

$$Q_t = K_H t^{\frac{1}{2}} \quad (3)$$

Where:

Q_t is the cumulative amount of drug released at time (t) and Q_0 is the dose of the drug incorporated in the delivery system.

K_0, K_1 and K_H are rate constant for zero order, first order and Higuchi model, respectively.

R_0^2, R_1^2 and R_H^2, square of release data for 12 h, fitted to zero order, first order and Higuchi equations respectively, were calculated and used to compare the release kinetics of different formulations.

To introduce the release kinetics as response in the design, we use the ratio between R_0^2 to R_1^2 or R_H^2. If the result was more than one, the release follows a zero order model. Otherwise, it follows either first or Higuchi model.

The results of ANOVA for different batches of coated formulations are calculated using Design-Expert® version 8.0.6 software and they are statistically significant at p-value <0.05. For further confirmation, the contribution percentage (PC %) of each factor in the response was calculated using the following equation [22]:

$$PC\% = \frac{SS_P}{SS_{total}} \times 100 \quad (4)$$

Where SS_p is the purified sum of squares and is given by SS-Residual. SS is the individual sum of squares, Residual is the sum of squares of error and SS_{total} is the total sum of squares. The largest PC% value indicates the most significant influence of the considered response.

The average response for each factor was computed at each level and labeled as k_i, where i represent a level.

In order to evaluate and compare dissolution data of the optimized CBZ-EOP tablets and the marketed CBZ-ER tablets, the dissolution profiles were statistically analyzed using dissolution similarity factor f_2 [23], calculated using the following equation:

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n} + \sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (5)$$

Where, n is numbers of dissolution time point

R_t is the reference dissolution point at time t

T_t is the Test dissolution point at time t

The f_2 value between 50 and 100 suggest that the dissolution is similar. The f_2 values of 100 suggest that the test and reference profile are identical and as the value becomes smaller, the dissimilarity between releases profile increases.

3. Results and discussion

3.1. Solubility of CBZ in the physical mixture of PVP K30 and SLS

The CBZ solubility was found to be 238.64 μg/ml. As shown in Table 3, CBZ in all PMs showed higher saturation solubility as compared to pure one. Among various CBZ-PMs, PM2 and PM3 containing a combination of polymer and surfactant (PVP K30, SLS) showed higher saturation solubility, which was increased as the SLS fraction was raised in the PM. Although it is well known that the PVP K30 will form a soluble complex with the drug [16], it was evident that the amount of PVP K30 as used in PM1 could not induce noticeable increase in CBZ solubility. Since it reduces the surface tension of the drug particles, SLS in combination with PVP K30 improves the wettability and contributes to further solubility enhancement. Further, adding small amounts of SLS (20–40 mg) inside the tablet core were expected to locally increase the solubility of CBZ whereas the same amount if added to the dissolution media will not result in the same solubility enhancement. Therefore, through the combining effects of solubility enhancement of both PVP K30 and SLS we were able to formulate CBZ in EOP tablets with improved release pattern. According to the above studies, PM3 was used for the optimization of tablet core formulation.

Table 3 – CBZ Solubility in different ratio of CBZ-PMs.

Physical mixture	Code	Ratio	Saturation solubility (μg/ml)[a]
Pure CBZ	CBZ	1	238.64 ± 3.3
CBZ/PVP K30	PM1	1:0.5	300.49 ± 2.7
CBZ/PVP K30/SLS	PM2	1:0.4:0.1	410.45 ± 2.9
CBZ/PVP K30/SLS	PM3	1:0.3:0.2	519.84 ± 3.6

[a] The values represent the Mean ± SD (n = 3).

3.2. Optimization of tablet core formulation

Parameters which were selected to optimize the core formulations included the type and amount of both osmotic agent and swellable polymer. The composition of each formulation was shown in Table 1 and their release profiles were illustrated in Fig. 1 and Fig. 2.

3.2.1. Effect of type and amount of osmotic agent

It was reported that the drug release from osmotic tablets was directly proportional to the difference in osmotic pressure generated within the system [4]. Fig. 1A showed the release profile of a formulation containing 200 mg of mannitol (F1), KCl (F2) or fructose (F3) as osmotically active agents. Interestingly, the highest release rate, about 68% at 24 h, with highest R_0^2 value (0.9882) was obtained with mannitol, which has a lowest osmotic pressure (38 atm) as compared with KCl (245 atm) and fructose (355 atm), whereas KCl exerted unexpected low release rate. These results might be explained by the fact that KCl would be dissociated to K+ and Cl− and these ions interacted or adsorbed to others ingredients in the core tablet, the alkali cation (K+) would react with the SLS to form insoluble crystals of potassium lauryl sulfate (KLS) [24]. Therefore the amount of KCl to induce the osmotic pressure of the solution inside the tablets might be reduced and consequently the rate of water flow into the tablet and the release of drug reduced, since the driving force for the drug release in this dosage form is the osmotic pressure. In addition, the

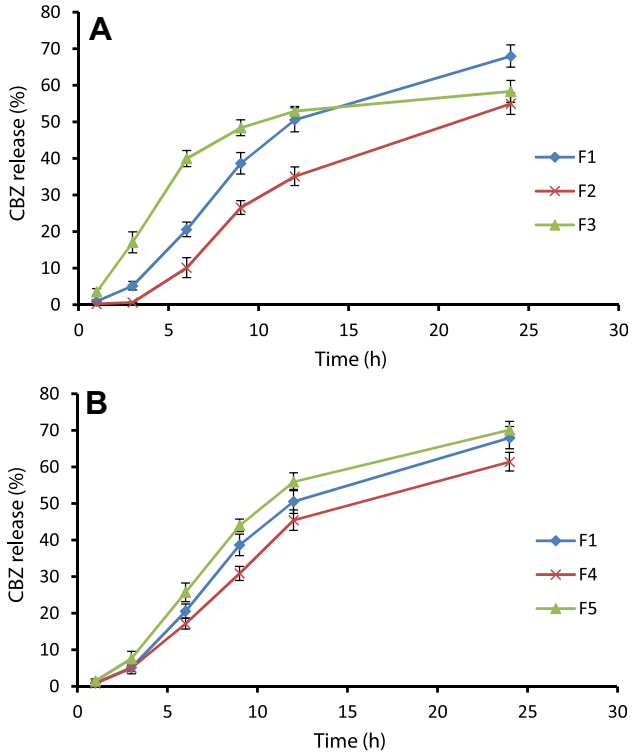

Fig. 1 – Release profile from CBZ-EOP tablets containing different osmotic agent: (A) types and (B) concentrations, (Mean ± SD, $n = 3$).

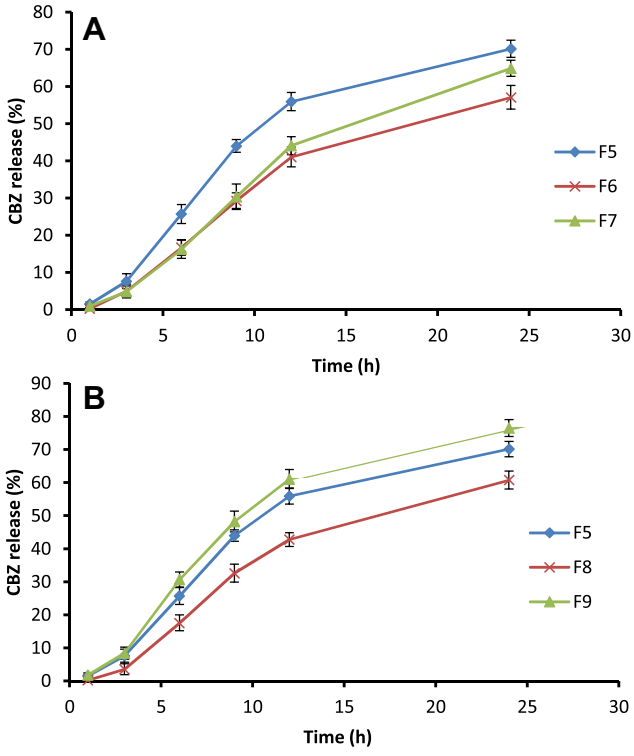

Fig. 2 – Release profile from CBZ-EOP tablets containing different polymer: (A) types and (B) concentrations, (Mean ± SD, $n = 3$).

solubilizing effect of SLS will be reduced also; as a result the overall release will be decreased.

On the other hand, when fructose was used as osmotic agent, high and fast drug release in the first nine hours (48%) was obtained, as comparing to mannitol (38%) and KCl (26%). It was reported that drug release from osmotic devices continue until the osmotic pressure between inside and outside environment becomes equal [25]. Thus, we assume that cessation of water/drug movement across the SPM was occurred (58% at 24 h) as a result of faster equilibrium in the osmotic pressure created by fructose as compared to the other osmogents and this is due to its highest osmotic pressure associated with its concomitant release with the drug. Therefore mannitol was chosen as osmogent for further investigation.

To study the influence of mannitol amount on CBZ release rate, tablet core was prepared with different amounts of mannitol. Fig. 1B illustrated that the release rate of CBZ increased significantly with the increase of mannitol amount from 150 to 250 mg with no effect on the release kinetics which still follows zero order pattern. The more the mannitol incorporated, the more water was imbibed and the more the drug was released. Therefore the amount of mannitol which was adopted for further investigation was 250 mg (F5).

3.2.2. *Effect of type and amount of polymer*

To examine the effect of polymer type on CBZ release, different core formulations were prepared by using the same amount, 50 mg per core tablet, of HPMC with different MW, hence different viscosities; 5 cp, 100 cp and 100,000 cp for HPMC E5, HPMC K100LV and HPMC K100M, respectively. Fig. 2A showed that at 24 h the highest release rate, 70%, was obtained by using HPMC of the highest viscosity, K100LV (F5), whereas the lowest release rate, 57%, was obtained by the lowest viscosity, E5 (F6). For the release kinetics, the highest and the lowest viscosity HPMC obtained nearly similar values of R_0^2. These results indicate that the polymer type had no significant effect on the release kinetics of CBZ from the prepared formulations. HPMC of low MW, such as E5, swelled and dissolved quickly to give a solution of both low viscosity and expanding force [8]. Therefore the driving force of drug release form the device would be small. Whereas HPMC of a higher MW swelled well, increased the inner viscosity, the expanding force and hence the drug release rate, as observed with F5. However, if the MW of HPMC was greatly increased, such in the case of HPMC K100M, the slower release was observed (F7) due to the high viscosity of the system and the formation of gel layer, which would obstruct the drug molecule diffusion. Also it is previously reported that polymer with high viscosity might close the drilled orifice and hindered the drug release [8].

Fig. 2B showed that drug release rate increase by increasing the polymer amount from 25 mg to 75 mg. High amount of HPMC K100LV attains the appropriate viscosity and suitable expanding force for the system. It was also observed that the polymer amount did not affect the release kinetics as indicated by the similarity of R_0^2 values of all formulations. In conclusion, apart from osmotic pressure, the polymer swelling is another driving force for the drug release [8,26]. Therefore to get the required release profile, HPMC (K100LV) in

the amount of 75 mg was used for further investigation of the coating parameters.

3.3. Optimization of SPM formulations

To insure the ER properties of osmotic pump delivery system, the core formulations are usually coated by semi-permeable polymer coats. Parameters which were selected to optimize the polymer coat included the type and amount of plasticizer, coat thickness and orifice size. Table 4 showed the structure of Taguchi OAD and the obtained results of drug release. The average k_i for the each studied factor was illustrated in Fig. 3 and the results of ANOVA analysis were tabulated in Table 5.

3.3.1. Effect of type and amount of plasticizer

When the CA–acetone solution is used alone for core coating, the SPM will be ruptured easily during the drug release. Thus in order to improve the SPM physical properties and film-forming characteristics, plasticizers were usually incorporated into the coating solution [27]. As they can also affect the permeability of the polymers films, it is important to investigate their effects on drug release [8,28].

Fig. 3A showed that increase in PEG grade from 400 to 2000 lead to increase in drug release and its deviation from zero order kinetics. The higher the PEG molecular weight, the bigger the size of the formed pores after PEG leaching [27], and hence the higher release rate and the more diffusion obtained. Similar results were obtained in previous study [29] where the drug release rate from enteric coated microporous osmotic tablets was increased with the increase in PEG grade. The result of ANOVA showed that the PEG type is statistically significant and contributes to the release rate. However, this effect is limited to the first 12 h when the PEG is present in an effective concentration in the tablet coat, after that the remaining amount will not significantly contribute to the release. As expected the PEG grade also contributed to the release kinetics by (PC%, 4.11%).

Fig. 3B showed that increase in PEG amount would increase the drug release rate and the deviation of the release profile to Higuchi kinetics. Because of its hydrophilicity, PEG leaches easily and can create a porous structure, which increases membrane permeability and drug release rate [26]. The result of ANOVA indicated that PEG amount was statistically significant and represent the most influencing factor on both the release rate and kinetics by its highest PC values as compared to other factors, so the optimization of plasticizer amount could be considered as critical for the optimization of the release behavior form the osmotic device.

3.3.2. Effect of SPM thickness

By separating the tablet inside from its outside, the SPM represents a very important parameter in the osmotic device. Fig. 3C showed that the drug release was inversely proportional to the coat weight gain. This can be attributed to the fact of increasing the SPM thickness will lead to increase its resistance to imbibe the dissolution medium and lower the dissolving rate of the tablet core components which consequently reduces drug release rate from osmotic devices [11,26]. The results of ANOVA indicated that this factor is statistically significant during 12 h and beyond this time point become less significant, however, the PC% indicates it still have considerable contribution until 24 h. This study revealed also that SPM thickness contributed to the release kinetics by (PC%, 21.86%). Increase the SPM thickness will reduce the drug diffusion by increasing the diffusional layer thickness and hence lead to increase in the tendency of following zero order kinetics. The SPM thickness is crucial to provide the appropriate quantity of water in the tablet core in the appropriate time and to assure that the pressure produced during swelling does not lead to rupture of the system so its optimization is very important for approaching a desirable release profile.

3.3.3. Effect of orifice size

Fig. 3D showed that there is no significant change in the release parameters due to the change in orifice size from 0.1 to 0.8 mm. The results of ANOVA analysis indicated that this factor is statistically insignificant ($P > 0.05$) and is not contributing to the release rate and kinetics (PC, 0%). Similar results were reported on osmotic devices of nifedipine [30], naproxen [31] and indomethacin [8] in which there was no significant difference in release rate of drugs from their osmotic devices having the orifice size from 0.25 to 1.41, 1 to 1.5 and 0.35 to 0.55 mm, respectively. However, it should be noted that the orifice size has no effect on the drug release only within certain range. Hydrostatic pressure could be developed within the core if the orifice size is too small and solute diffusion may occurred if it is too large [32]. It can be concluded that in this study the orifice size plays no role in the mechanism of drug release which was directed by other formulation factors.

Table 4 – Design matrix based on OAD L9 and measured responses.

Run	Factors				Release rate (%)				Release kinetics
	A	B	C	D	3 h	6 h	12 h	24 h	$R_0^2/(R_H^2$ or $R_1^2)$
1	2	3	1	2	29.1	46.2	86.85	93.2	0.9899
2	3	1	3	2	2.76	11.5	29.8	71.1	1.2418
3	3	2	1	3	20.4	47.5	78.5	97.3	0.9895
4	2	1	2	3	1.39	9.36	36.4	72.3	1.1991
5	3	3	2	1	22.5	43.02	82.8	92.3	0.9985
6	1	1	1	1	2.69	15.17	35.5	76.9	1.1918
7	2	2	3	1	8.90	21.9	40.2	81.9	1.1901
8	1	3	3	3	10.9	30.03	54.6	86.07	1.1348
9	1	2	2	2	5.70	22.7	50.2	80.8	1.1575

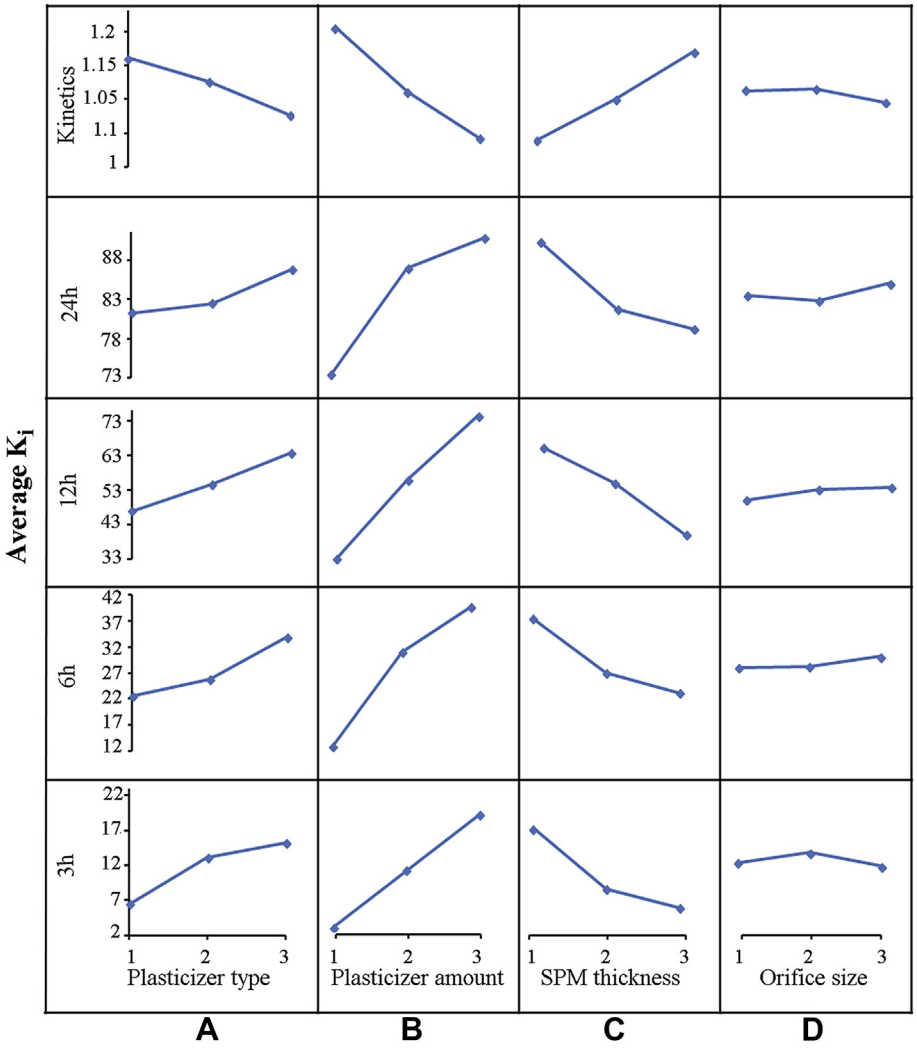

Fig. 3 – Average response at each level (k_i) of: (A) plasticizer type, (B) plasticizer amount, (C) SPM thickness and (D) orifice size for release rate and kinetics.

3.4. *Optimum formulation and its release kinetics*

The optimum formulation in which the core contains 60 mg of PVP K30, 40 mg of SLS, 250 mg of mannitol, 75 mg of HPMC K100LV and coated with 3% of CA containing a 60% of PEG 400 with an orifice of 0.1 mm diameter, was found to deliver, 21.16% at 3 h, 45.41% at 6 h, 79.14% at 12 h and 96.34% at 24 h of CBZ from the osmotic device.

The optimum formulation showed also that zero order had the higher regression value compared to the first and Higuchi kinetics in the following order; R_0^2 (0.9917); R_1^2 (0.8902); R_H^2 (0.9668), which indicates that the release of CBZ from the prepared EOP tablets predominantly follows zero order kinetics for 12 h.

Fig. 4 and the analysis of the similarity factor f_2 which was equal to 70 (greater than 50) clearly suggest the similarity between the prepared CBZ-EOP tablets and Tegretol CR 200 tablets for the release of CBZ. Although this similarity, CBZ-EOP formulation is expected to have an extra-advantages because of its independent release of physiological factors such as gastric motility and pH and hence represents an effective therapy tool with less fluctuations in drug levels

Table 5 – ANOVA analysis and PC% for each factor in the OAD L9 matrix.

Responses	A		B		C		D	
	p-value	PC%	*p*-value	PC%	*p*-value	PC%	*p*-value	PC%
3 h	0.016	11.65	0.002	73.72	0.013	14.04	1	0
6 h	0.02	8.03	0.003	73.71	0.012	17.39	1	0
12 h	0.07	7.78	0.011	66.34	0.03	22.89	1	0
24 h	0.28	0	0.014	60.95	0.09	10.95	1	0
Kinetics	0.06	4.11	0.02	42.06	0.029	21.86	1	0

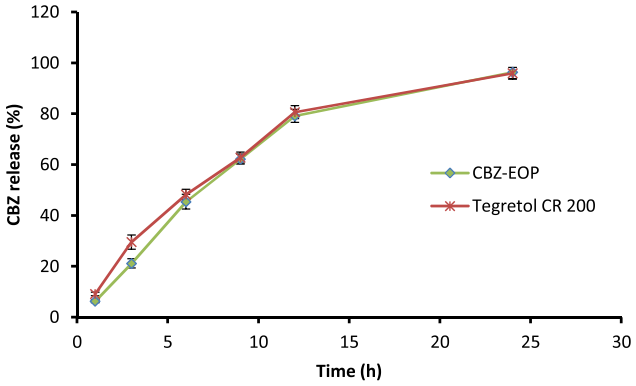

Fig. 4 – Release profile from CBZ-EOP tablets and Tegretol CR 200 tablets, (Mean ± SD, $n = 3$).

especially for patients suffering from some inflammatory bowel diseases characterized by low intestinal pH [33] or in cases of variation in gastric emptying rate due to different physiological, pathological or pharmacological factors [34].

4. Conclusion

New design of EOP tablet with a combined solubility enhancers and a swellable polymer had been successfully prepared for extended delivery of CBZ. The combination of a hydrophilic polymer with surfactant as solubility promoter and the use of swellable polymer as drug pushing system represent a new and effective approach for the delivery of poorly water-soluble CBZ to be formulated in a simple and cost effective method as EOP tablet. In this study, we extensively examined the effect of each of the tablet core and coat component and its contribution to the release behavior and the optimized formulation revealed that in order to have a good osmotic system; we have to carefully select the swellable polymer, osmotic agent, plasticizer, and SPM thickness. The optimized tablets showed satisfactory USP limits with high similarity to the marketed product Tegretol CR 200 and up to 80% drug release at a rate of approximately zero order for up to 12 h, which indicate that the release pattern was independent of drug load. The results obtained demonstrate the possibility of expanding the application field of this new EOP tablets as controlled drug delivery systems to poorly water-soluble drugs.

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