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Research Article

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Design and Characterization of Pregabalin Swellable Core Osmotic Pumps

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ABSTRACT

The present investigation concerns the development of osmotic pumps for a water soluble drug (pregabalin), using swellable core technology (SCT), that uses osmotic pressure and polymer swelling to deliver drugs to the gastrointestinal tract (GIT) in a reliable and reproducible manner. The SCT formulations consisted of a core tablet containing the drug and a water swellable component, and one or more delivery ports. All the formulations were prepared by direct compression method. The amount of polymers and osmogens to be incorporated in each formulation were decided by optimization technique. The current experiment was aimed to formulate matrix tablets using lactose, sodium carboxy methyl cellulose (sod.CMC), methyl cellulose (MC), hydroxypropyl methylcellulose (HPMC) and sodium starch glycolate (SSG) by direct compression method. The prepared matrix tablets were characterized for physical evaluations to indicate tablet uniformity and mechanical integrity. The in vitro and in vivo performance of Pregabalin, formulated and evaluated in two different SCT core configurations: homogeneous-core (single layer) and bi-layer core tablets. In vitro dissolution studies showed that the drug release rate was relatively independent of the core configuration but the extent of release was somewhat lower for the homogeneous-core formulation, particularly under non-sink conditions. The drug release profiles of all the formulations were subjected to all pharmacokinetic models such as zero order, first order, higuchi and Peppas models. Optimized formulation (F8) followed zero order kinetics with non-fickian diffusion mechanism (n>0.5).

Keywords: Pregabalin, swellable core technology, single layer, bi layer and tri layer core tablets.

INTRODUCTION

Controlled release drug delivery systems (CRDDS) of drugs have recently become an important field of research because of their extended and safe use [1]. Among various controlled release devices, osmatically driven system holds a prominent place because of their reliability and ability to deliver the contents at a predetermined rate for prolonged period of time [2-3]. In osmotic drug delivery many types of osmotic pumps are there, but in this project we used swellable core technology (SCT) in osmotic drug delivery systems showed in Figure 1.

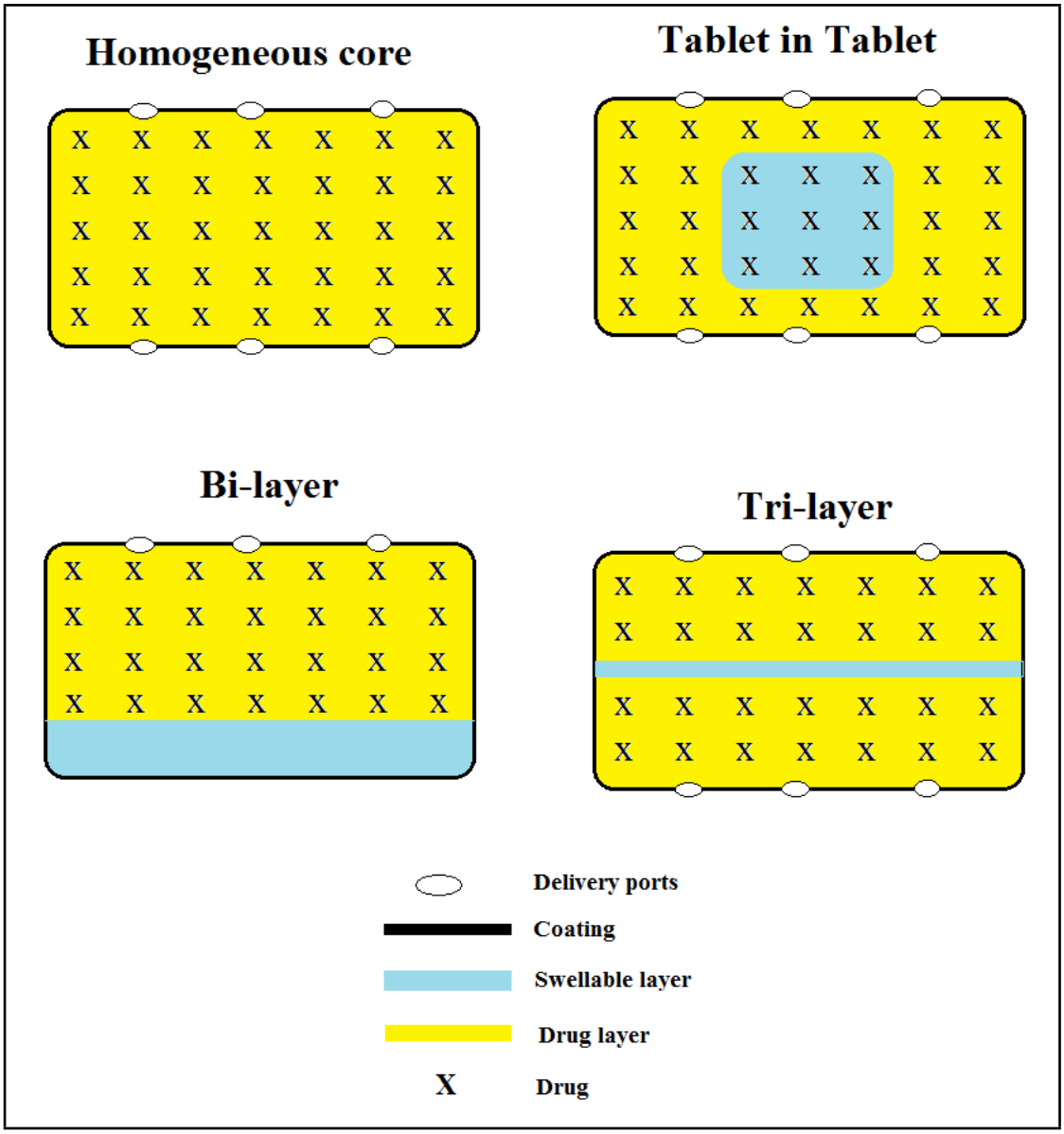

Figure 1. Schematic diagrams of four SCT formulations: Homogeneous core (single), tablet in tablet (TNT), bi-layer and tri-layer core tablets

SCT was developed as a drug delivery platform that can deliver drugs with moderate to poor aqueous solubility over an 8 to 24 hours period [4-5]. SCT formulations consist of a core tablet that contains a drug composition and a water swellable composition [6-7]. Various physical and chemical approaches have been applied to produce a well characterized dosage form that controls drug input into the body within the specifications of the desired release profile. This is generally accomplished by attempting to obtain "zero-order" release from the dosage form, i.e., the rate of drug release is independent of the drug concentration [8-9]. Extended-release systems generally do not attain this type of release and usually try to mimic zero-order release [10]. Also factors like pH, presence of food, and other physiological factors may affect drug release from conventional CR systems (matrix and reservoir). Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs [11-12]. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible modulate the release characteristics by optimizing the properties of drug and system [13-14]. At the same time, they can also be utilized to deliver drugs at a controlled and predetermined rate. Pregabalin is an anticonvulsant (is an anti-epileptic drug), freely soluble in water. Pregabalin binds to calcium channels on nerves and may modify the release of neurotransmitters (chemical that nerves use to communicate with each other) and reducing communication between nerves may contribute to pregabalin effect on pain and seizures. Pregabalin may be taken with or without food. The initial dose for neuropathic pain associated with diabetic peripheral neuropathy is 50 mg, 3 times a day (150 mg/day) and the dose may be increased to maximum dose of 100 mg, 3 times a day (300 mg/day) after one week [15]. The purpose of this work was to formulate a solid dosage form system (tablets) for pregabalin using the principles of

osmosis. It was planned to formulate the 2 types of osmotic drug delivery system such as homogeneous core and bi-layer core tablets.

MATERIALS AND METHODS

Material

Pregabalin received as a gift sample from Abhinandan Rasayan Private Limited, Thane and Maharashtra, India. Hydroxypropyl methylcelluloses (HPMC), polyvinylpyrrolidone (PVP) K30, methyl cellulose (MC), sodium carboxy methyl cellulose (sod.CMC) were received from DOW chemical company, USA. Lactose, cellulose acetate, magnesium stearate and talc were purchased from S.D. Fine Chem. Ltd., Mumbai, India.

Analytical Method

Construction of calibration curve of Pregabalin

The λ_{max} of pregabalin in 0.1N HCl was scanned and found to have the maximum absorbance at 210nm. The standard graph of pregabalin in 0.1N HCl was plotted by taking concentration ranging from 5-30 µg/ml and a good correlation was obtained with R^2 value of 0.993.

Preparation of swellable core osmotic pump tablets

Direct compression

Swellable core osmotic tablets of pregabalin were prepared by using different additives of sodium CMC, MC, SSG, HPMC and PVP K30 as polymers and lactose as a diluent. MC and PVP K30 also used as osmotic agents. The weighed quantities of drug and polymers were in different ratios and tablets were prepared by direct compression method. (Table 1)

Homogeneous core tablets preparation method

Accurately weighed quantities of polymers and PVP K30 were taken in a mortar and mixed geometrically, to this required quantity of pregabalin was added and mixed slightly with pestle. The powder was passed through sieve no. ≠40 and mixed with the drug blend which was also passed through sieve no.≠40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this, magnesium stearate was added and mixed for 5 minutes; later talc was added and mixed for 2 minutes. The mixture equivalent to 500 mg was compressed into tablets with 12 mm round concave punches at a hardness of 6-8 kg/cm^2.

Bilayer core tablets preparation method

PVP K30 was taken in a mortar and mixed geometrically, to this required quantity of pregabalin was added and mixed slightly with pestle. The powder was passed through sieve no. ≠40 and mixed with the drug blend which was also passed through sieve no.≠40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this, magnesium stearate was added and mixed for 5 minutes; later talc was added and mixed for 2 minutes. The mixture equivalent to 300 mg was compressed into tablets with 12 mm round concave punches at a hardness of 5-6 kg/cm^2. Then take required quantity of polymer in a plastic bag and the mixture equivalent to 200 mg was compressed in to tablets with 12 mm round concave punches at a hardness of 4-5 kg/cm^2. Then take two tablets and compressed into 1 tablet with two layers 12 mm concave punches at a hardness of 6-8 kg/cm^2. The composition of various formulations was given in Table 1.

Table 1. Formulae used to prepare pregabalin swellable core osmotic tablets

Samples	F1	F2	F3	F4	F5	F6	F7	F8
Pregabalin	50	50	50	50	50	50	50	50
PVPK30	50	50	50	50	50	50	50	50
Lactose	285	235	285	235	310	260	310	260
Sodium CMC	100	150	-	-	-	-	-	-
Methyl cellulose	-	-	100	150	-	-	-	-
Sodium starch glycolate	-	-	-	-	75	125	-	-
HPMC	-	-	-	-	-	-	75	125
Magnisium stearate	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10

Drug excipients compatibility studies

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure drug and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide and compressed to form a KBr disk. The samples were scanned from 4000 to 400 cm^{-1}.

Physical properties of prepared powder blends

The physical properties like bulk density, tapped density, Carr's index (CI), Angle of repose were evaluated for the prepared powdered blend.

Physical evaluation of matrix tablets

The compressed tablets were assessed for weight variation, hardness, friability and drug content. To compute the weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (Shimadzu, Japan) and determined the average weight and deviation. Tablet hardness (n=6) was determined using Monsanto tablet hardness tester. Friability was calculated using ten tablets with the help of Roche friabilator (Electro lab, India).

Determination of drug content uniformity

Drug content uniformity was estimated by crushing randomly picked ten tablets. The drug powder equivalent to 100 mg of pregabalin was extracted to the drug solution with suitable solvent. To extract the drug solution, drug powder was soaked in 10 ml of ethanol for one hour, filtered and the resultant clear drug solution was added to simulated gastrointestinal fluid and diluted in a suitable manner to gain 10 mg/ml solution. Then the 10 mg/ml drug solution (n=3) were measured for pregabalin content at 210nm using UV-Visible spectrophotometer and calculated the drug content uniformity. Similar procedure was used for all the formulations.

***In vitro* dissolution study**

In vitro drug release studies were carried out using USP XXIV Type II dissolution apparatus (Electro lab, TDT-08L) in simulated gastrointestinal fluids at standard conditions i.e., 50 rpm rotation speed and 37±0.5 ^{0}C temperature. The dissolution study was performed by using 0.1 N HCl for 8 h. At specific time intervals (0.5h, 1h, 2h, 4h, 6h and 8h), 5 ml samples were collected and restored by an equal volume of fresh pre-warmed dissolution medium. Then the collected samples were diluted suitably and determined the pregabalin content using UV-visible spectrophotometer at 210nm.

RESULTS AND DISCUSSION

Drug excipients compatibility study

The drug excipients compatibility study was carried out by using FTIR. The FTIR spectral analysis of pure pregabalin (Figure 2) and optimized formulation (Figure 3) were showed the principal peaks at similar wave numbers. And in optimized formulation some different wave numbers observed. However, these additional peaks were observed with physical mixtures, which could be due to the presence of polymers. These results suggest that there is no interaction between the drug and polymers used in the present study.

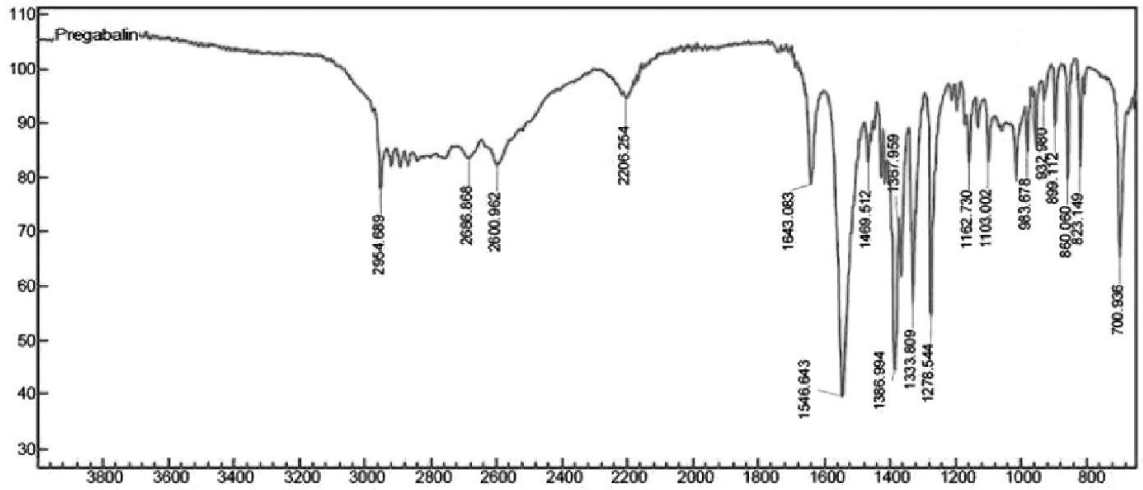

Figure 2. Fourier transforms infrared spectra of pure pregabalin

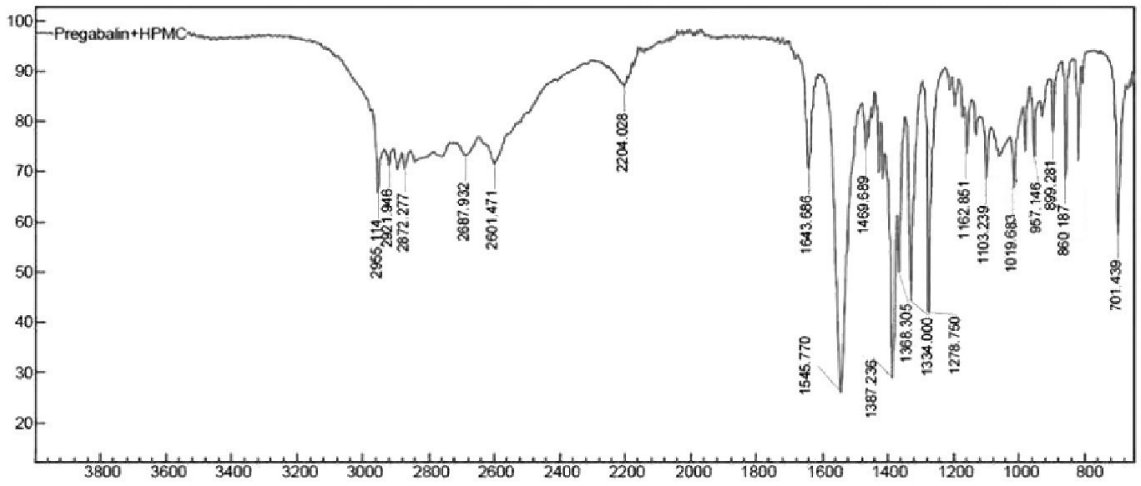

Figure 3. Fourier transforms infrared spectra of optimized formulation (F8)

Physical properties of prepared powder blends

Table 2 shows the different physical properties like bulk density, tapped density, Carr's index (CI), Angle of repose for powder blend. All the formulations were found within the pharmacopoeial limits.

Table 2: Physical properties of powder blends of tablet formulations

Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Angle of repose (^{o})
F1	0.385±0.14	0.450±0.18	14.42±0.14	27.14±0.18
F2	0.362±0.11	0.421±0.70	14.01±0.11	28.49±0.10
F3	0.381±0.13	0.452±0.31	15.70±0.13	28.92±0.31
F4	0.389±0.10	0.446±0.53	12.78±0.12	29.44±0.53
F5	0.392±0.30	0.443±0.88	14.51±0.30	29.82±0.88
F6	0.401±0.19	0.474±0.42	15.40±0.19	30.10±0.42
F7	0.398±0.13	0.452±0.91	13.94±0.13	30.12±0.91
F8	0.390±0.14	0.462±0.22	15.58±0.14	30.35±0.22

The prepared tablets were evaluated for its hardness, weight variation, friability and drug content shown in Table 3.

Table 3. Physical evaluation parameters of tablets

Batch	Weight Variation (mg) (n=20)	Hardness (kg/cm^2) (n=6)	Thickness (mm) (n=10)	Friability (%) (n=10)	Drug Content (%) (n=6)
F1	501±1.34	6.4±0.06	3.86±0.05	0.28±0.05	97.93±1.4
F2	500±2.67	7.2±0.01	3.76±0.16	0.34±0.02	98.48±1.9
F3	503±1.98	7.1±0.12	3.88±0.23	0.32±0.16	98.13±2.4
F4	502±2.34	6.8±0.09	3.56±0.12	0.25±0.06	98.26±2.6
F5	501±2.89	6.1±0.18	3.63±0.07	0.23±0.14	97.91±3.1
F6	502±1.89	6.8±0.12	3.55 ±0.16	0.22±0.12	98.49.±1.7
F7	502±2.36	7.4±0.18	3.68±0.15	0.21±0.03	98.74±3.2
F8	500±0.98	7.0±0.09	3.65±0.25	0.26±0.03	97.89±1.9

Evaluation of physical parameters of swellable core osmotic tablets

Table 3 shows the different physical parameters that were evaluated for prepared matrix tablets. The weight variation of the tablets was found in the range of 500±0.98 mg (F8) and 503±1.98 mg (F3) and all the formulation tablets were fell within the pharmacopoeial limit i.e., average weight±5%. The thickness and diameter of prepared tablets was found as 3.55 ±0.16 mm (F6) and 3.88±0.23 mm (F3) respectively. The hardness of the tablets was found between 6.1±0.18 kg/cm^2 (F5) and 7.4±0.18 kg/cm^2 (F7). All the formulations were found below the 1% friability that indicated the tablet mechanical strength. The tablets were found to contain not less than 98% and not more than 100% of the labelled amount indicating the drug content uniformity. From these results, the prepared tablets complied with Indian pharmacopoeial limits. From the physical characterization, all the tablet formulations were found to be uniform in weight variation, hardness and drug content and within the limits of friability.

***In vitro* drug release studies**

All the formulations (F1-F8) of different concentration of the polymers were evaluated for the *in vitro* drug release studies. The results were reported and showed in the following Figures 4 and 5.

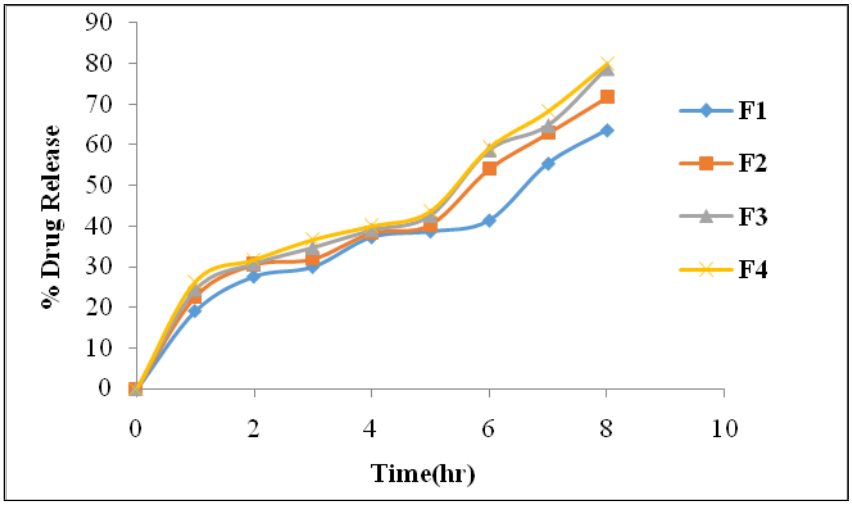

Figure 4. *In vitro* drug release of homogeneous core swellable core osmotic tablets containing sodium carboxy methyl cellulose and methyl cellulose

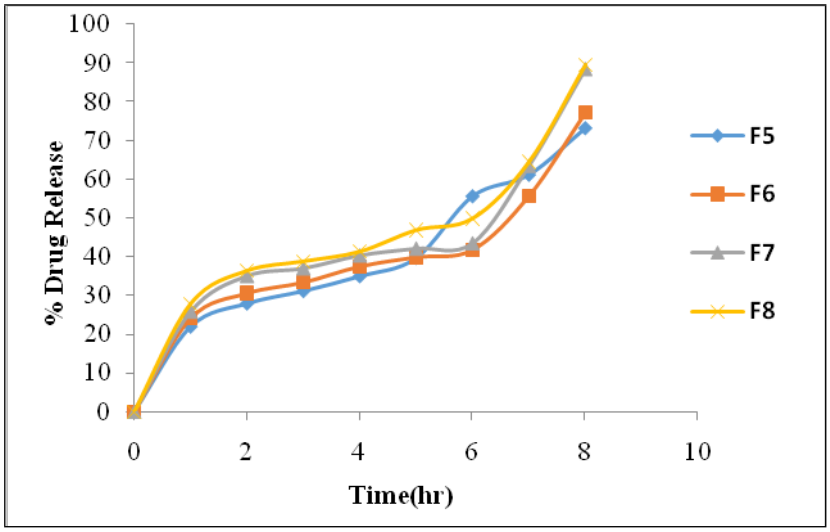

Figure 5. *In vitro* drug release of bi-layer core swellable core osmotic tablets containing sodium starch glycolate and hydroxypropyl methylcelluloses

The variation in drug release was due to different polymer concentrations in all the eight formulations. The cumulative drug release was shown in Figure 4 and Figure 5. In first four formulations F1, F2, F3 and F4, comparing F1and F2, from F2 formulation released more drug. And F3 and F4, from the F4 formulation drug more released, homogeneous core tablet formulations which were depends up on polymer concentrations. In case of F5, F6, F7, F8 formulations F6 and F8 were released more drug, these also depend up on polymer concentrations which bi-layer core osmotic tablets. In the eight formulations best one was HPMC containing formulation. Formulations F1, F2, F3 and F4 composed of sodium CMC, and MC, showed a release of 63.7%, 71.63%, & 78.72%, 79.82% in 8hr respectively. However, formulations F5, F6, F7, F8 containing SSG and HPMC, showed a release of 73.31%, 77.2%, 88.38%, 89.48% respectively met the desired drug release profile in 8hr. From the eight formulations F4 and F8 showed maximum drug release i.e., 79.82%, 89.48% in 8hr. Therefore F4 and F8 formulations considered as the best formulations in two methods among all the formulations. From these two formulations, depending up on the drug release rates F8 was found to be best formulation.

Mechanism of drug release and kinetics

The drug release data of pregabalin matrix tablets were fitted into different kinetic models representing zero order, first order, higuchi and peppas model to know the release mechanism. F1, F2, F4, F5 and F8 followed zero order, whereas F3 and F6 followed higuchi. Further F7 followed peppas model. In all the formulations, the diffusion exponent value is greater than 0.5. The optimized formulation (F8) followed the peppas model (R^2=0.992) with non-fickian mechanism. The correlation coefficients (R^2) of all the formulations were shown in Table 5.

Table 5: Results of correlation coefficients (R^2) and diffusion exponent (n) of release data of pregabalin by curve fitting method

Formulation code	R^2				n
	Zero order	First order	Higuchi	Peppas	
F1	0.984	0.698	0.962	0.839	0.538
F2	0.988	0.719	0.958	0.850	0.569
F3	0.972	0.678	0.978	0.845	0.517
F4	0.996	0.719	0.982	0.989	0.601
F5	0.991	0.693	0.979	0.887	0.582
F6	0.986	0.684	0.989	0.912	0.589
F7	0.980	0.702	0.972	0.986	0.542
F8	0.998	0.715	0.983	0.992	0.615

***In vitro* buoyancy studies**

In order to develop the desired swellable core osmotic pumps of pregabalin, it was necessary to optimize the release rate of the drug. The optimized formulation which slow down the water diffusion inside the dosage form and provided a prolonged drug release over a predetermined period of time.

All the formulations remain buoyant for more than 8 h in dissolution medium. The *in vitro* buoyant of F4 and F8 formulations were shown in Figure 6 and 7 respectively.

Figure 6. Homogeneous core tablet (a), after one hour (b), after three hours (c), after five hours (d) and after eight hours (e)

Figure 7. Bilayer Core Tablets (a), after one hour (b), after three hours (c), after five hours (d) and after eight hours (e)

CONCLUSION

Pregabalin was successfully formulated as osmotic pump tablets to release drug at zero order release up to 8 hrs. Overall, the current work has indicated that it is indeed possible to develop an effective and safely scalable formulation. Swellable core technology (SCT) represents a broadly applicable oral osmotic drug delivery platform for the controlled release of drugs. The formulations consist of a drug containing composition and water swellable composition. This can be designed in several different configurations. SCT formulations are components that are safe and commonly used in pharmaceutical products, and are available in pharmaceutical grades. The processes for manufacturing SCT formulations are somewhat more complex.

The above results clearly indicates the feasibility to develop swellable core osmotic pumps of highly water soluble drugs exempting the complex tableting technology associated with the Two types of osmotic tablets. The drug release from these systems were influenced by the factors such as solubility and osmotic pressure of the core compound, membrane nature and size of delivery orifice, which can be easily optimized to get the desired release rate. Still, considering the limited sample size, the results are at best indicative and further clinical work can be undertaken to be developed commercially.

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