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FORMULATION AND EVALUATION OF PREGABALIN FILMS

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INTRODUCTION

CONTROLLED RELEASE DRUG THERAPY

For many years the treatment of acute or chronic sicknesses were carried out normally via the transport of medication to sufferers through diverse pharmaceutical forms encompass pills, pills, creams, suppositories, drinks, ointments, aerosols and injectables. Even these days, those conventional dosage paperwork are the main vehicles pharmacists usually visible inside the prescription and non-prescription drug market. The kinds conventional oral drug shipping systems are regarded to provide a set off launch of the drug. Therefore to reap as well as to hold the drug awareness within the range of healing effectiveness required for the treatment, it's miles frequently vital to take this kind of drug shipping gadget several instances an afternoon. This interprets into a extensive fluctuation of the drug tiers frequently with a sub-healing and/or poisonous ranges and waste of drugs. Recently, numerous technical advances have resulted inside the development of latest drug delivery systems able to controlling the rate of shipping of medicine, preserve the period of the therapeutic activity and cognizance the delivery of medication to a tissue.[1]

A controlled release of the for management of the system usage and dosage form of the oral route is designed for flexibility and attention. The design of the delivery system for oral controlled release delivery system, such as the types of considerable importance are related to each other, multiple variables in the treatment of the disease is the patient to the treatment length, and drug property.

Controlled Release of 2 means that the system is capable of some real therapeutic control to indicate whether it is the temporal or spatial nature or both. In other words, the system tries to

maintain a constant concentration of active agents in the target tissue to make available. It is this kind of this system that is different from the sustained release systems.

Advantages of CONTROLLED release dosage form[3]

- **Improved patient compliance** and convenience due to less frequent drug administration.
- **Reduction in fluctuation** in steady state levels and therefore, better control of disease condition and reduction intensity of local or systemic side effects.
- **Increased safety margin** of high potency drugs due to better control of plasma levels.
- **Maximum utilization of drug** enabling reduction in total amount of dose administered.
- **Reduction in health care costs** through improved therapy, shorter treatment period, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients.
- **Sustained blood levels**; the size and frequency of dosing are determined by the pharmacokinetic and pharmacodynamic property of drug. The use of CONTROLLED releaseproducts may maintain therapeutic concentration over prolonged period.
- **7. Attenuation of adverse effect**, the use of CONTROLLED release products avoids the high initial blood concentration, which may cause many side effects like nausea, local irritation, haemodynamic changes etc.

Disadvantages of CONTROLLED release dosage form[3]

- Toxicity due to dose dumping.
- Increased cost.
- Unpredictable and often poor *in vitro- in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counseling.
- Increased potential for first- pass clearance.

Plan of work for pregabalin films

1. Selection and purchasing of medication
2. Construction of conventional bend of pregabalin
3. Selection of plastic

4. Selection of plasticizer
5. Selection of transmission enhancer
6. Preparation of matrix patch
7. Evaluation of ready formulationsPhysico – chemical evaluation parameters.

Physico – substance assessment parameters

- Physical appearance
- Folding endurance
- Thickness of the patch
- Weight uniformity
- Flatness
- Drug content
- Percentage wetness uptake
- Percentage wetness content

a. In - vitro tissue layer permeation research by Keshary-Chien diffusion mobile using dialysis tissue layer.
b. In - vitro tissue layer permeation research was fixed in to kinetic modelling of medication launch.

PREGABALIN FILMS

Development of Pregabalin films

Preparation of backing HPMCP membrane

The membrane was prepared by the cast film technique. HPMCP was soaked in 15 ml of alcohol-acetone in 1:1 ratio and held for hours. To this remaining amount of solvent and tri-ethyl citrate (plasticiser) was added. The solution was cast into molds of glass of specific sizes, and then air dry.

Preparation of Pregabalin films

The films of pregabalin were prepared using the method of casting solvent with different viscosity grades of polyethylene oxide (PEO), such as 301, PEO PEOPEO coagulant and 303. Separate films were prepared using the method for the preparation of the film is illustrated in figure 1. The polymer PEO was soaked in the mixture of ethanol and dichloromethane in 50: 50 ratios. Added to all of this is the mixture of triethyl citrate as a plasticizer. Each formulation was prepared for the 5 movies at the same time with repetitions of six times to

the reproducibility. The final solution was then poured into molds of glass of required size and allowed to air dry for 24 hours to complete evaporation of the solvent. Three different concentration of each formulation with each formulation was prepared. A total of 9 formulations were prepared and evaluated by various parameters. The formulation of the prepared pregabalin films are summarized in Table 6.1.

Table 1. Formulation table of Pregabalin films.

Ingredients	P-1	P-2	P-3	P-4	P-5	P-6	P-7	P-8	P-9
	mg/5 films per 1 mould								
Pregabalin	375	375	375	375	375	375	375	375	375
PEO WSR 301	500	750	1000	-	-	-	-	-	
PEO Coagulant	-	-	-	500	750	1000	-	-	-
PEO WSR 303	-	-	-	-	-	-	500	750	1000
Ethanol*	10	10	10	10	10	10	10	10	10
Dichloromethane*	10	10	10	10	10	10	10	10	10
Triethyl citrate in ml	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Talc	10	10	10	10	10	10	10	10	10
Total/5 Films	875	1125	1215	715	965	1215	715	965	1215
Weight of Each film (Th)	175	225	275	175	225	275	175	225	275
Weight of Each film (Pr)	172.3	225.6	276	173.4	224.3	274.9	174	226.1	275.3

Lamination of pregabalin films with backing HPMCP layer.

Loaded the drug pregabalin PEO films were prepared by the lamination process. The posterior layer HPMCP was taken separately; a few ml of acetone, alcohol along with the right mix of triethyl citrate as a plasticizer was sprayed in the posterior layer and wait a few seconds for fast nature of the layer. Then both layers laminated were mutually and dried at room temperature for the evaporation of the remaining solvent. Figure 5.1 describes the method for the preparation of oral movies.

In-Vitro Drug Release Studies

In vitro dissolution studies were carried out with the Pregabalin films prepared with the PEO WSR 301.

The results of *in vitro* dissolution and release kinetics of the prepared pregabalin films with PEO WSR 301 were summarized in the table no. 6.25. Figure no. 6.27 shows the plot of the cumulative % release Vs time of plot of pregabalin films prepared with PEO WSR 301.

Pregabalin films prepared with the PEO Coagulant

The formulations of the prepared films were evaluated for various physico chemical properties.

In-Vitro Drug Release Studies

In vitro dissolution studies were carried out with the Pregabalin films prepared with the PEO Coagulant.

The results of *in vitro* dissolution and release kinetics of the prepared pregabalin films with PEO Coagulant were summarized in the table no. 6.27. Figure no. 6.28 shows the plot of the cumulative % release Vs time of plot of pregabalin films prepared with PEOCoagulant.

Differential scanning calorimetey (DSC) Study

Thermal properties of pure drug was evaluated by means of differential analysis (DSC) caloriemetry using a diamond (DSC) (Mettler star SE 8.10). Exactly heavy 5-6 mg samples were hermetically sealed in aluminum pots and heated at a rate of 50 OC/min from 500C to 300 0C temperature range under nitrogen at a rate of 25 ml/min. DSC thermogram pure pregabalin is given in figure no. 6.77 and with PEO is given in figure no. 6.71.

Fourier transforms infrared Radiation measurement (FT-IR)

FTIR study on the selected formulation prepared with a combination of different polymers as pure poly pregabalin and ethylene oxide. The peak of the spectrum of the formulation of points were similar with that of the purity of the pregabalin, clearly indicating that there is no drug-polymer interaction. FTIR spectra of pure pregabalin is given in Figure n° 6.72 and with the figure of PEO no.6.73.

RESULTS AND DISCUSSION

PREGABALIN FILMS

Characterization of Active Pharmaceutical Ingredient, Pregabalin

Pure Pregabalin was characterized for Bulk density, Tapped density, Compressibility index and Hausner's ratio.

Based on the results of the flow properties the drug Pregabalin was having fair flow property and required to improve the flow property to avoid the process problems arising during the compression and preparation of various dosage forms.

Table 2. Bulk properties of the Pure Pregabalin.

Sl.No	Parameters	Pregabalin
1	Bulk density	0.444 g/ml
2	Tap density	0.740 g/ml
3	Compressibility index	40
4	HR Ratio	1.667

In Vitro Dissolution Studies of Pregabalin Films Prepared With the PEO WSR 301

Table 3. Dissolution data of Pregabalin prepared with PEO WSR 301.

Time (Hrs)	P-1	P-2	P-3
0	0	0	0
1	44.4	36	26.1
2	68.8	59	46.6
3	81.5	74.2	64.3
4	91.3	83.7	76
5	98	92.7	85.4
6		96.9	90.2
7		99	94.4
8			97.5
9			99.7
10			
11			
12			
13			
14			

Table 4. Release kinetics data of Pregabalin prepared with PEO WSR 301.

Release Kinetics data			
	P-1	P-2	P-3
Zero order	0.9369	0.9004	0.8815
First order	0.9472	0.9649	0.8968
Higuchi	0.9758	0.9605	0.9542
Peppas	0.982	0.9698	0.9581
Peppas(n)	0.4922	0.5231	0.6049

***In Vitro* Dissolution Studies of Pregabalin Films Prepared With the PEO Coagulant**

The Drug release in vitro was faster in the formulations prepared with less content of polymers (P-4) and the complete liberation of drugs around the 98 % was observed in the period of 7 hours. The formulations prepared with the greatest concentration of 301 WSR PEO extended the release of drugs up to 9 hours (P-5). The release was extended until 10

hours in formulation of P-6, which is the largest concentration of polymer coagulant PEO. The maximum release was 10 hours with POE coagulant. The dissolution of the data was studied by the release kinetics. The in vitro release kinetics were calculated and the values of the Correlation coefficient of zero order release kinetics were found 0.8764 to 0.8786, the values of the Correlation coefficient to release the first order kinetics were found 0.9741 to 0.9987. On the basis of the above results the drug release was followed by the release of the first order. The release kinetics of the prepared formulations was found your first order with diffusion mechanism. Peppas n indicates the release mechanism Fickian diffusion is anomalous. Table 6.5 summarizes the physical-chemical properties of preparations with PEO WSR coagulant. Table 6.27 summarizes the data of in vitro dissolution.

Table 5. Dissolution data of Pregabalin prepared with PEO Coagulant.

Time (Hrs)	P-4	P-5	P-6
0	0	0	0
1	36.3	28.9	22.2
2	60.7	52	41.3
3	76	67.7	58.7
4	86.2	79.2	70.2
5	93.5	87.1	79.8
6	96.6	92.4	84.6
7	99	94.4	89
8		97.4	92.7
9		99	94.9
10			98
11			
12			
13			
14			

Table 6. Release kinetics data of Pregabalin prepared with PEO Coagulant.

Release Kinetics data			
	P-4	**P-5**	**P-6**
Zero order	0.8764	0.8517	0.8786
First order	0.9715	0.9783	0.9987
Higuchi	0.9447	0.935	0.9619
Peppas	0.9578	0.9445	0.964
Peppas(n)	0.5154	0.5478	0.6562

***In Vitro* Dissolution Studies of Pregabalin Films Prepared With the PEO WSR 303**

Table 7. Dissolution data of Pregabalin films prepared with PEO WSR 303.

Time (Hrs)	P-7	P-8	P-9
0	0	0	0
1	32.8	23.5	17.4
2	53.5	41.4	34.9
3	70.9	59.1	47.8
4	82.5	70.5	60.4
5	87.7	78.7	68.7
6	92.7	84.8	76.1
7	95.1	87.1	81.9
8	97	91.4	85.4
9	99	94.5	89
10		97	91.4
11		97.6	93.7
12		99	95.5
13			97.6
14			99

Table 8. Release kinetics data of Pregabalin films prepared with PEO WSR 303.

Release Kinetics data			
	P-7	**P-8**	**P-9**
Zero order	0.8356	0.8376	0.8643
First order	0.9803	0.9956	0.9993
Higuchi	0.9228	0.9609	0.9863
Peppas	0.9439	0.9627	0.9754
Peppas(n)	0.4962	0.6294	0.7352

Evaluation parameters of prepared Pregabalin prepared with PEO WSR 301, PEO Coagulant, PEO WSR 303.

Table 9. Evaluation parameters of prepared Pregabalin prepared with PEO WSR 301.

Evaluation Parameters	**P-1**	**P-2**	**P-3**
Thickness (mm)	0.38±0.03	0.46±0.01	0.51±0.01
Folding endurance	>300	>300	>300
Drug content	98±1.1	97±1.2	97±1.6

Table 10. Evaluation parameters of prepared Pregabalin prepared with PEO Coagulant.

Evaluation Parameters	P-4	P-5	P-6
Thickness (mm)	0.39±0.01	0.47±0.02	0.50±0.02
Folding endurance	>300	>300	>300
Drug content	99±2.1	99±2.2	98±1.1

Table 11. Evaluation parameters of prepared Pregabalin films prepared with PEO WSR 303.

Evaluation Parameters	P-7	P-8	P-9
Thickness (mm)	0.39±0.01	0.45±0.01	0.53 ±0.01
Folding endurance	>300	>300	>300
Drug content	99±1.5	99±1.4	99±1.3

Photomicrographic study of the Pregabalin films prepared with PEO 303.

Table 12. % drug content of accelerated stability study samples of Pregabalin films at 40°C/75% RH.

Formulation	P-9
Estimated (%)	
Initial	99.0
40°C/75% RH 1 M	98.1
40°C/75% RH 2 M	98.4
40°C/75% RH 3 M	99.5
40°C/75% RH 6 M	98.3

Fourier transforms infrared Radiation measurement (FT-IR)

The spectrum peak points of the formulation were similar with that of the pure Pregabalin, clearly indicating that there is no drug-polymer interaction.

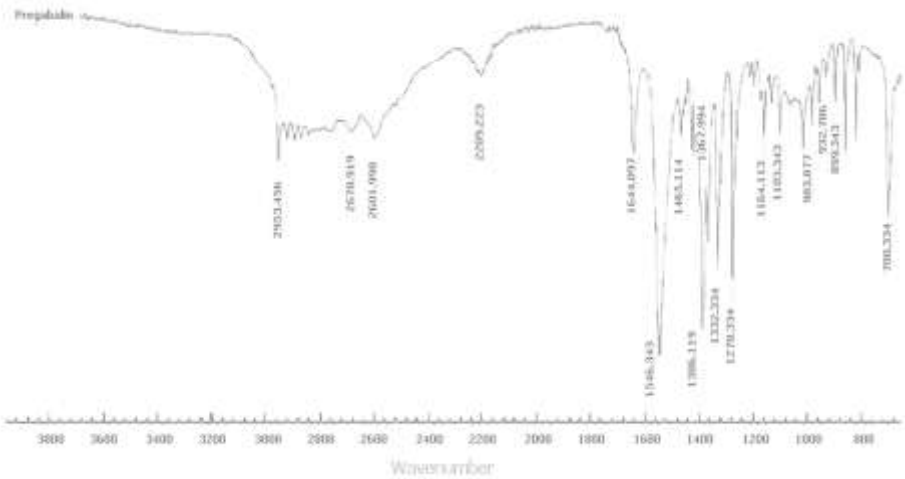

Fig 1. FTIR spectrum of Pregabalin pure drug.

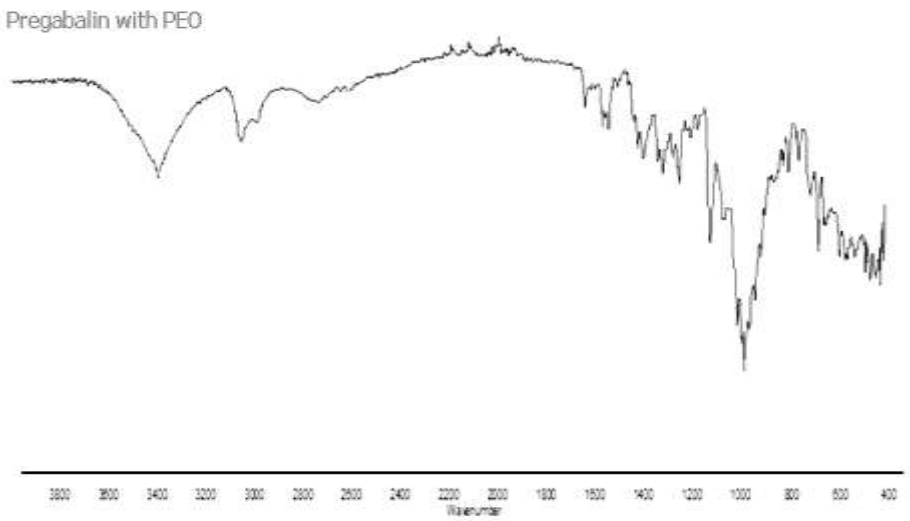

Fig 2. FTIR spectrum of Pregabalin and Poly ethylene oxide.

CONCLUSION

Epilepsy affects up to 1% of the population. Despite antiepileptic drug (AED) treatment, up to one third of patients continue to experience seizures. 1 Pregabalin (PGB) is the latest compound that joins the list of approved "new" AEDs. In addition to epilepsy, it has demonstrated efficacy for the treatment of neuropathic pain and generalised anxiety disorderPGB is an effective and well-tolerated novel oral therapy for epilepsy, neuropathic pain and GAD. It has so far received approval for the treatment of the first two conditions. Effective doses appear to range from 150 to 600 mg/day. With its good efficacy and tolerability, favourable pharmacokinetic profile and low risk of drugdrug interactions, PGB is a welcomed addition to the armamentarium for the treatment of these common disorders. It is hoped that accumulated experience will further optimise its use so that more patients can lead safer and more fulfilling lives.

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