RESEARCH ARTICLE

Formulation, Optimisation and Evaluation of Levodopa and Entacapone Loaded Transdermal Patches for the Treatment of Parkinson's Disease

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ABSTRACT

Parkinson's disease is an extrapyramidal motor disorder leading to progressive degeneration of neurons in substantia niagra, pars compacta and the dopaminergic tract. The most promising drugs used to treat Parkinson's disease, i.e., levodopa and entacapoe have very low oral bioavailability because of first-pass metabolism, therefore to increase the bioavailability of levodopa and entacapone, these were incorporated in transdermal patches. Different formulations of the levodopa and entacapone drugs were prepared with different polymeric ratios, by using the solvent casting method and the formulations were evaluated for *in-vitro* and *in-vivo* tests, which focus on drug release and drug excipient compatibilities. Various models were applied to ascertain the kinetics of drug release by using *in-vitro* release data. Nine formulations were prepared and evaluated out of which F6 was found to be the best formulation, which contained HPMC and ethyl cellulose in the ratio of 2:3. It showed drug release of 99.11% in about 12 hours.

Keywords: Parkinson's disease, Levodopa, Entacapone, Transdermal patches.

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INTRODUCTION

Transdermal drug delivery (TDD) refers to the delivery of drug transdermally or *via* the skin for local action of systemic circulation.[1,2] The main advantage associated with the transdermal dosage form is it eliminates associated variables of the oral route of drug administration, transdermal route bypasses the GI absorption, first-pass metabolism and localized effect. Also, delivery of drugs through the skin has many advantages: a larger surface area for absorption, sustained release of a drug, reduced dosing frequency, rapid termination of treatment when needed, reduced fluctuation in plasma drug concentration and increased bioavailability.[3-5]

Parkinson's disease is a neurological disorder widely spread worldwide. It is a progressive degenerative, extrapyramidal motor disorder causing degeneration of neurons in substantia niagra, pars compacta and the dopaminergic tract. Degeneration of neurons leads to a decrease in the level of dopamine in the striatum corneum, which is responsible for muscle tone and also plays an important role in the coordination of movement.[6] It mostly affects older people. It is characterized by muscular rigidity, hypokinesia and tremors followed by defective posture, difficulty walking, and diminished facial expression accompanied by dementia.[7,8] This results in dopamine deficiency in the striatum, which controls muscle tone and coordinates movements. Levodopa is the precursor of dopamine and is considered to be the first-line treatment of Parkinson's disease.[7-9] It crosses the blood-brain barrier (BBB) and reaches to dopaminergic neurons, which converts it to dopamine and, store it and release it as a transmitter.[9]

The major disadvantage of levodopa is that it has a half-life of 1.5 hours and its oral dose has low bioavailability due to extensive hepatic first-pass metabolism. This disadvantage of oral levodopa leads to the need of transdermal delivery of levodopa so as to avoid first-pass metabolism.[9,10] Entacapone on the other hand inhibits COMT, thus inhibiting the conversion of levodopa to 3 methyldopa before crossing the blood-brain barrier. This ultimately helps the conversion of levodopa to dopamine post-blood-brain barrier. Thus, incorporating the combination of these two drugs in transdermal patches (TDP) increases the bioavailability of levodopa and etacapone. In addition, transdermal patches also help maintain the unfluctuating plasma drug concentration for a prolonged period.[11-13]

The aim of the present work is to formulate and evaluate transdermal patches of levodopa ad entacapone so as to increase the bioavailability of drugs and also patient compliance. TDP

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Table 1: List of materials and their manufactuers

S. No.	*Materials used*	*Grade*	*Manufacturer*
1	Levodopa	Pharma Grade	Swapnaroop Pvt. Ltd,(Aurangabad, India).
2	Entacapone	Pharma Grade	Swapnaroop Pvt. Ltd., (Aurangabad, India).
3	Ethyl Cellulose	Pharma Grade	CDH, Pvt Ltd, Mumbai
4	HPMC	K100M	CDH, Pvt Ltd, Mumbai

(Transdermal patches) were formulated by using polymers in different ratios by solvent casting method.

MATERIALS AND METHODS

List of materials and their manufactuers as shown in Table 1.

Identification and Compatibility Studies[14,15]

Before formulating drug-loaded transdermal patches, Identification studies like FTIR and UV analysis were carried out to establish the physicochemical properties of the drug and its compatibilities with other excipients for the formulation of transdermal patches. Pure drugs and polymers were analysed separately and then the mixture of drug and polymer was analyzed for the determination of λ max by using UV spectrophotometer (SHIMADZU 1800). The sample was scanned in 200 to 400 nm range in, and lambda max was observed. FTIR studies using ATR FTIR were performed to examine the interaction of levodopa and entacapone with HPMC and ethyl cellulose. The sample was taken and placed under the FTIR spectrometer and the peaks were observed under the range of 600 to 4000 nm.

Formulations of Transdermal Patches

In the current research, levodopa and entacapone loaded matrix type transdermal patches (TDP) were formulated using the solvent casting method. Nine batches with different ratios of polymers hydroxy propyl methyl cellulose and ethyl cellulose were formulated and evaluated.[16,17] Levodopa (300 mg) was added to the solution of HPMC and entacapone (200 mg) was dissolved in the solution of ethylcellulose.[17,18] Now both the solutions were mixed with uniform stirring and as a plasticizer 30% w/v propylene glycol was added to the solution.[19,20] For penetration enhancement, 5% w/v Tween-80 was used.[21] The solution was homogenized and sonicated for 10 minutes for proper mixing and to remove air bubbles if any, in the mixture. 10 mL solution was taken in a petri dish (previously waxed with glycerine) and dried at room temperature. After drying, patches were taken out from the petri dish and was cut into 2 cm^2 patch and stored well in an air-tight container till further use.[21,22] Transdermal patches with different concentration ratios of polymer and their evaluation is shown in Table 2.

Evaluation of Transdermal Patches[11,12,23]

Thickness

Previously cut six pieces of the polymeric film having 2 cm^2 were taken and thickness was measured by using digital vernier caliper. The thickness uniformity was measured at five different sites and the average was calculated.

Table 2: Composition of levodopa and entacapone loaded transdermal patches with different polymer concentration ratio

Batch code	*Polymers ratio (HPMC:EC)*	*Permeation enhancer % w/v*	*Solvent system*
F1	1:1	30	Water and ethanol
F2	1:2	30	Water and ethanol
F3	1:3	30	Water and ethanol
F4	2:1	30	Water and ethanol
F5	2:2	30	Water and ethanol
F6	2:3	30	Water and ethanol
F7	3:1	30	Water and ethanol
F8	3:2	30	Water and ethanol
F9	3:3	30	Water and ethanol

Folding endurance

It was determined by repeatedly folding the patch in one place till it broke. The number of times the patch was folded at the same place without breaking gave the value of folding endurance. The same procedure was repeated with six pieces of the polymeric film having 2 cm^2.

Tensile strength

The tensile strength was determined by the apparatus designed. The instrument was designed such that it had a horizontal wooden platform with a fixed scale and attachments for two clips that hold the transdermal patch under test. Out of the two clips,, one was fixed and the other was movable. Weights were hung to one end of a pulley and the other end of the pulley was attached with a movable clip. The tensile strength was measured six times with six pieces of polymeric film and the value was noted as the weight applied on 2 cm^2 patch till it broke. The tensile strength was calculated using a formula.

$$Tensile strength = \frac{\text{Force applied to break film (kg)}}{\text{Cross section area (cm}^2\text{)}}$$

Weight variation

The test was performed by calculating the average weight of 10 patches and then weighing each patch individually. The individual weight should be within limits (as per the average weight).

Moisture content

About 2 cm^2 of patch was weighed accurately and placed in a dessicator containing $CaCO_3$ carbonate for a day (24 hours). It was reweighed and moisture content was determined by using formula:

$$Moisture\ content = \frac{Initial weight - Final weight}{Initial weight} \times 100$$

Drug content

A patch of 2 cm^2 was dissolved in 10 mL water: ethanol solvent system of ratio 1:1. From the above solution 1-mL sample was taken and the volume made up to 10 mL. The solution was analyzed under UV spectrophotometer at 280 and 390 nm for levodopa and entacapone, respectively and the concentration of the drug was determined by using a standard curve equation. Drug content was calculated using the following formula.

Table 3: Evaluation of different batches

Batch code	*Polymers ratio (HPMC:EC)*	*Thickness (mm)*	*Folding endurance*	*Tensile strength*	*Moisture content*	*Weight (mg)*	*Drug content %*	
							LD	*EC*
F1	1:1	0.128	>150	0.28 ± 0.02	3.82 ± 0.12	94.5 ± 3.52	96.15 ± 3.73	96.15 ± 3.78
F2	1:2	0.132	>150	0.43 ± 0.04	3.85 ± 0.13	93.8 ± 4.17	96.2 ± 4.16	97.52 ± 3.45
F3	1:3	0.139	>150	0.52 ± 0.01	3.93 ± 0.09	94.3 ± 3.32	96.32 ± 3.22	98.32 ± 3.22
F4	2:1	0.148	>150	0.35 ± 0.03	4.21 ± 0.10	96.4 ± 2.53	98.1 ± 3.09	97.51 ± 4.19
F5	2:2	0.151	>150	0.48 ± 0.02	4.39 ± 0.12	96.6 ± 3.42	98.37 ± 3.87	97.69 ± 2.83
F6	2:3	0.154	>150	0.62 ± 0.01	4.46 ± 0.14	96.8 ± 3.23	98.43 ± 4.94	98.73 ± 4.07
F7	3:1	0.163	>150	0.39 ± 0.01	5.34 ± 0.15	98.3 ± 4.31	98.79 ± 4.65	97.69 ± 4.16
F8	3:2	0.165	>150	0.52 ± 0.02	5.51 ± 0.04	98.73 ± 4.35	98.86 ± 3.28	97.73 ± 3.43
F9	3:3	0.168	>150	0.69 ± 0.03	5.62 ± 0.05	98.83 ± 3.94	98.94 ± 3.36	98.95 ± 3.58

Table 4: Stability studies of TDP

Formulation	*% drug remaining*											
	4 week				*8 week*				*12 week*			
	25˚C and 60% RH		*40˚C and 75% RH*		*25˚C and 60% RH*		*40˚C and 75% RH*		*25˚C and 60% RH*		*40˚C and 75% RH*	
	LD %	ECN %	LD %	ECN %	LD %	ECN %	LD	ECN	LD	ECN	LD	ECN
F4	96.2	97.52	91.12	94.31	95.01	96.22	87.52	91.67	94.58	95.81	84.92	88.26
F5	98.37	97.69	94.33	95.02	97.77	96.48	91.30	90.21	95.75	94.36	88.21	87.53
F6	98.43	98.73	95.01	95.98	97.52	97.47	94.19	92.66	96.17	96.86	91.30	90.58

$$Drug\ content = \frac{Actualdrugconcentration}{Concentrationofdrugtaken} \times 100$$

Stability studies[23]

Stability studies were conducted as per ICH guidelines. In this study, 3 selected batches were stored at room temperature and elevated temperature for three months. The degradation of the drug was checked at the first, second and third monthss.

In-vitro drug release studies[24,25]

The tests on selected patches were performed *in-vitro* by using freshly obtained goat's skin as a biological membrane. As the dissolution medium, phosphate buffer (PB-7.4) was taken. The patches were applied on the goat's skin and studied using Franz diffusion cell. The temperature of the assembly was maintained at 32ºC. This assembly was set aside for 24 hours and samples were taken at regular time intervals of 1-hour. These samples were examined for UV absorbance at 280 and 390 nm, respectively for levodopa and entacapone.[26] To study the drug release mechanism, the final optimized batches were subjected to different kinetic models such as zero order, first order, matrix diffusion Higuchi, Hixon-Crowell, and Korsmeyer-Peppas.[27-29]

RESULTS AND DISCUSSION

Identification and Compatibility Studies

Identification studies like FTIR and UV analysis showed the compatibility of excipients and polymers with drugs. Caliberation curve for levodopa and entacapone was constructed and no notable change was found.

Evaluation of TDP

Different physicochemical properties like folding endurance, thickness, tensile strength, moisture content, and content of drug present were evaluated for prepared patches. The results are shown in Table 3.

Stability Studies

Stability studies were performed on three selected batches on the basis of drug release profiles. At room temperature, no remarkable changes are observed for twelve weeks. While at elevated temperature, drug degradation was found to be higher. The results are shown in Table 4.

In-vitro Drug Release Studies

In-vitro drug release study was performed on all formulations. The results are shown in Tables 5 and 6 and graphical representation is illustrated in Figures 1 and 2 for levodopa and entacapone, respectively.

To study the mechanism of drug releas, final optimized batches were subjected to different kinetic models like zero order, first order, matrix diffusion Higuchi, Hixon Crowell, and Korsmeyer Peppas. The mechanism of drug release was determined by knowing the value of the regression coefficient. The regression coefficients for levodopa were found to be zero order: 0.883, first order: 0.972, Higuchi: 0.996, Hixon-Crowell: 0.990 and Korsmeyer-Peppas model: 0.995. The regression coefficient for entacapone was found to be 0.883 for zero order, 0.972 for first order, 0.951 for Higuchi, 0.990 for Hixon Crowell and 0.995 for the Korsmeyer-Peppas model. The regression coefficient value for both drugs was maximum for the matrix

Table 5: *In-vitro* drug release studies of levodopa

Time (Hours)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
1	27.3	25.6	24.2	26.01	26.8	25.89	15.6	10.9	8.2
2	29.01	28.1	26.14	32.4	30.4	29.56	18.12	14.00	10.6
3	35.6	34.01	32.10	35.71	34.11	34.33	23.45	21.6	18.19
4	48.8	46.2	41.4	46.02	42.1	39.34	28.3	24.32	21.66
5	60.1	56.1	55.5	52.21	49.00	43.12	32.14	29.8	26.23
6	70.26	63.6	63.2	61.3	56.7	51.25	39.7	33.9	31.67
7	83.1	80.2	79.83	75.7	68.7	58.64	46.2	36.8	34.5
8	89.31	83.6	81.10	87.2	75.89	73.8	55.1	39.2	38.15
9	92.4	88.9	84.2	90.12	82.13	79.5	58.9	43.87	41.64
10	97.4	97.1	95.3	94.6	91.23	89.67	64.9	48.2	45.12
11	98.2	95.00	94.3	97.23	92.67	96.75	69.2	56.34	52.43
12	-	-	97.12	97.31	97.42	99.11	75	65.46	58.9

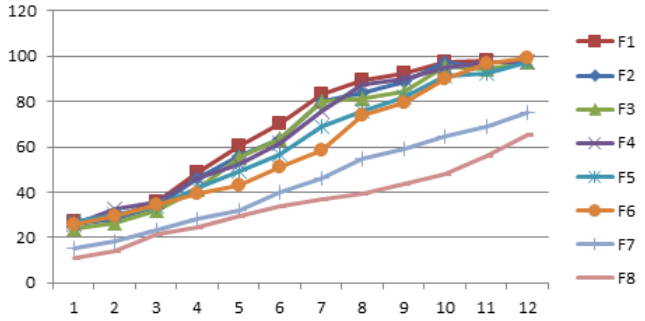

Figure 1: *In-vitro* drug release studies

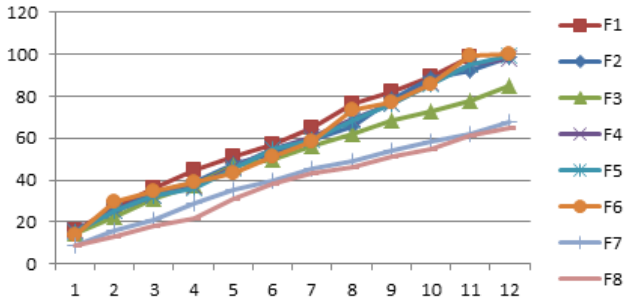

Figure 2: *In-vitro* drug release studies of entacapone

Table 6: *In-vitro* drug release studies of entacapone

Time (Hours)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
1	16.2	15.14	14.9	15.99	15.6	14.1	9.1	8.8	8.2
2	27	25.27	22.32	25.5	25.52	29.56	15.9	13.1	12.9
3	36.1	34.01	31.26	32.6	32.6	34.33	21.2	18.04	16.1
4	44.56	38.9	37.34	37.1	36.15	39.34	28.6	22	21.6
5	51.2	47.3	46.8	46.12	45.2	43.12	35.5	31.05	26.23
6	57.1	52.6	50.11	55.13	54.7	51.25	39.4	38.12	31.67
7	65	58.8	56.25	60.2	59.08	58.64	45.3	43.16	38.02
8	76.45	65.4	62.12	69	68.1	73.8	49.2	46.21	41.3
9	82.13	78.5	68.5	76.5	76.1	76.89	54.1	51.01	46.7
10	89.09	88.7	72.81	86.1	85.9	85.99	58.09	55.02	51.8
11	98.99	92.3	78.11	95.1	95.2	99.6	62.01	61.02	55
12	-	98.9	85	98.1	99.21	100	68.02	65.05	60

diffusion Higuchi model, which showed that drug release from patches followed the matrix diffusion Higuchi model.

The kinetic models and regression coefficient value of levodopa and entacapone for all the models are shown in Zero order release model of levodopa (Figure 3), First order release model of levodopa (Figure 4), Higuchi release model of levodopa (Figure 5), zero order release model of entacapone (Figure 6), first order release model of entacapone (Figure 7), higuchi release model of entacapone (Figure 8)

Release Model of Levodopa

Drug release kinetics and regression coefficient value of levodopa are shown in Table 7.

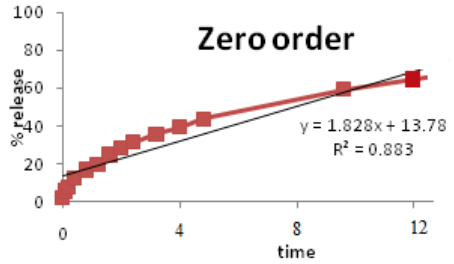

Figure 3: Zero order release model of levodopa

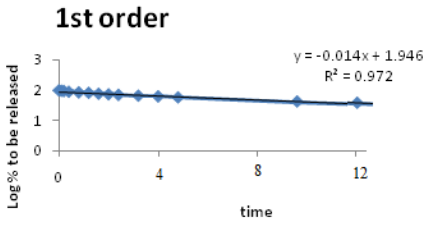

Figure 4: First-order release model of levodopa

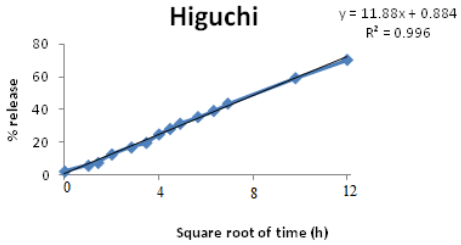

Figure 5: Higuchi release model of levodopa

Table 7: Release kinetics and regression coefficient of levodopa for different models

S. No.	*Release kinetic model*	*Regression coefficient (R^2)*
1	Zero-order	0.883
2	1st order	0.972
3	Higuchi	0.996
4	Hixon-Crowell root	0.990
5	Korsmeyer Peppas model	0.995

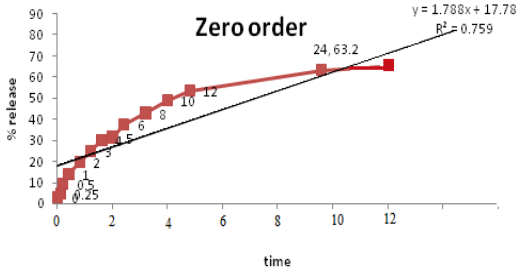

Figure 6: Zero order release model of entacapone

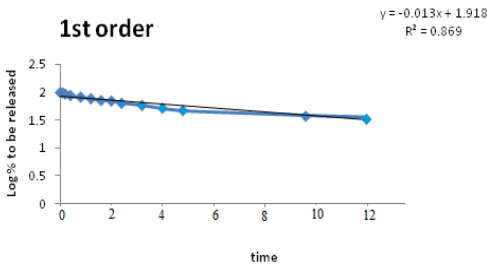

Figure 7: First order release model of entacapone

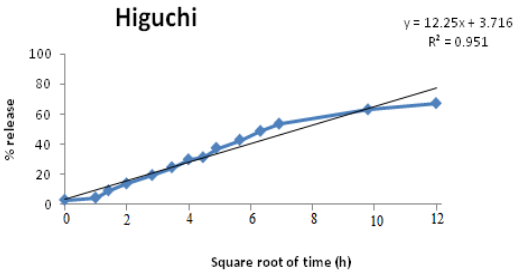

Figure 8: Higuchi release model of entacapone

Table 8: Release kinetics and regression coefficient of entacapone for different models

S. No.	*Release kinetic model*	*Regression coefficient (R2)*
1	Zero-order	0.759
2	1st order	0.869
3	Higuchi	0.951
4	Hixon-Crowell root	0.975
5	Korsmeyer Peppas model	0.966

Release Model of Entacapone

Drug release kinetics and regression coefficient value of entacapone is shown in Table 8.

DISCUSSION

The results revealed that the formulations prepared with different concentrations of ethyl cellulose and HPMC were uniform and had good surface morphology. The drug was distributed uniformly all over the patch. Other parameters were evaluated and on the basis of the results following inferences have been made:

The prepared patches were smooth, flexible and uniform in shape. The thickness of the films ranged from 0.128 to 0.168 mm. The highest thickness was found in F9, which clearly indicated that the thickness of the patch increased with the concentration and decreasing solubility of polymers.

Tensile strength ranged between 0.28 ± 0.01 to 0.69 ± 0.03 for batches F1 to F9, respectively. Studies have shown that tensile strength increases with increasing polymer concentration, especially ethyl cellulose. The folding endurance was found to be more than 150, which indicated that the patches prepared could withstand mechanical stress and were flexible. The percentage of moisture content ranged between 3.82 ± 0.12 and 5.62 ± 0.05. The moisture

content of various formulations increased with increasing concentration of polymers. Also, moisture content increases with the hydrophilicity of the polymer. The drug content in the formulation was in the range of 96.15 ± 3.73–98.85 ± 3.58**).** It was observed that the drug content in batches increased with increasing concentration of polymers. It may be due to higher drug entrapment by polymers. The polymer ratio didn't show any marked effect on drug content.

The best formulation was F6, which shows the optimum ratio of the polymers for the release profile. For the first 2 hours, conventional release and after that, for 12 hours, sustained release has been observed.

CONCLUSION

Transdermal patches were prepared by solvent casting method using hydrroxy propyl methyl cellulose (HPMC) and ethyl cellulose in various concentration ratios. For penetration enhancers, propylene glycol (PG) and Tween 80 were incorporated. All formulations were evaluated for various parameters, and it was found that all batches showed good physicochemical properties such as thickness, folding endurance, moisture content, and drug content. The *in-vitro* drug release study showed that the drug release from the patch is affected by the polymer concentration ratio. Optimized formulations were further screened for drug permeation studies. The effect of penetration enhancers was also studied. These studies indicated that the formulation with polymer ratio HPMC:EC (Batch F9 and F6) showed optimum drug release and incorporation of permeation enhancer further increased the diffusivity of drug from patches. The above patch gave the maximum drug release at 12 hours. F6 was considered to be the beast among all patches.

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