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Research Article

Development and Evaluation of Buccoadhesive Film of Ropinirole Hydrochloride for the Treatment of Parkinson's Disease

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ABSTRACT

The present research article represents the formulation and evaluation of buccoadhessive film of ropinirole hydrochloride. This drug is an oral non-ergoline dopamine agonist with the greater affinity at D3 receptor. This drug having low molecular weight (296.84 g/mol), and short biological half-life (4-6 hrs) which necessitates for multiple dosing for maintaining therapeutic effect throughout the day. Moreover, drug is metabolized in liver forming several inactive metabolites which decrease it oral bioavailability upto 50% making it a suitable candidate for administration of drug through buccal mucosa. Buccal films of ropinirole hydrochloride were prepared using various polymers (HPMC, EC, PVA and Carbopol) by solvent casting method using propylene glycol as plasticizer. These films were evaluated for various parameter such as appearance, surface texture, weight uniformity, thickness, folding endurance, surface pH, drug content and swelling index. All the formulations were subjected to *in vitro* drug release study which were carried out using egg membrane as semi permeable membrane.

Keywords: Ropinirole hydrochloride, buccoadhessive film, dopamine agonist, solvent casting, swelling index, *in vitro*.

INTRODUCTION

Parkinson's disease is a chronic progressive age related neurological disorder associated with the degeneration and destruction of neurons in the substantial nigra pars compacta (SN-PC) and nigrostratial (dopaminergic) tract which result in deficiency of dopamine in the striatum[1]. Parkinson's disease has four cardinal symptoms include bradykinesia (slowness and poverty of movement), muscular rigidity, resting tremor (which usually abates during voluntary movement), and an impairment of postural balance leading to disturbance of gait and falling. It is second most common neurodegenerative disease after alzimer's disease[2]. There are several treatment options available to reduce signs and symptoms of parkinson's disease and improve overall quality of life. These include monoamine oxidase type B (MAO-B) inhibitors, anticholinergic that shown to have mild effect, primarly tremors. carbidopa/levodopa is the most effective treatment options for parkinson's disease but the effectiveness of dopaminergic therapy is eventually limited by motor fluctuation and dyskinesia[3]. Non-ergoline dopamine receptor agonist ropinirole is currently recommended and shown to be efficacious in the treatment and reduction of motor fluctuation in patient with advanced Parkinsonism disease[1].

Ropinirole hydrochloride is a 4-[2-(dipropylamino) ethyl]-1, 3-dihydro-2*H*-indol-2-one; 4-[2-(di-*n*-propylamino) ethyl]-2(3*H*)-indol-2-one monohydrochloride[4] (Fig. 1). It is a non-ergoline D2/D3 dopamine agonist that binds to central and peripheral dopamine receptor. It has greatest affinity at D3 receptor[1,3]. It is weakly active at the 5-HT2, and α2 receptors and is said to have virtually no affinity for the 5-HT1, benzodiazepine, GABA, muscarinic, α1, and β-adrenoreceptors[5]. It is used to treat the signs and symptoms of idiopathic Parkinson's disease[6]. It is effective both as monotherapy as well as combination therapy with the reduce dose of levodopa[2]. It is present as oral immediate and prolonged release conventional dosage forms which are effective in treatment, suffers with the problem of frequent dosing due to short half-life (4-6 hrs) and low oral bioavailability[1,7] that decreases its therapeutic efficacy. To resolve these issues effectively an effective route and dosage form is required.

Among the various route of drug administration oral route is the most preferred and convenient route for systemic delivery of drug. Several advantages associated with it includes, painless, self-administration and reduced cost as compared to parenteral delivery[8].

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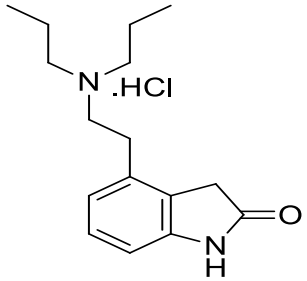

Figure 1: Ropinirole hydrochloride.

However, oral administration is limited by many disadvantages such as poor drug solubility or absorption, low bioavailability due to first pass metabolism, pH sensitive substances and peptide drug degradation in the harsh gastrointestinal environment and local gastro intestinal toxicity[4,8]. To overcome these obstacles transmucosal routes (e.g. ocular, oral, rectal, vaginal) has been developed as an alternative route for rapid drug absorption and successful delivery of drug into systemic circulation. Among the various transmucosal routes, oral mucosa has excellent accessibility, noni nvasive nature of administration, ease and convince of dosing, precise localization and permeable mucosa with a rich blood supply make it more attractive route for systemic drug delivery for extended period of time[9]. Oral mucosal provide potential route for large, hydrophilic and unstable proteins and peptides as well as conventional small drug molecules. Buccal route is preferred region as compare to sublingual route because buccal mucosa is less permeable and thus not able to elicit a rapid onset of absorption and hence better suited for sustained release action. Further it has immobile mucosa makes it more advantageous for retentive muccoadhesive systems[10].

Various bioadhesive mucosal dosage forms have been developed which includes adhesive tablet, adhesive gels and ointments, adhesive patches and adhesive films[11,12,13]. Buccal films and patches are convenient dosage forms due to small size and thickness which improves patient compliance[8]. They are preferred over adhesive tablets in terms of flexibility and patient comfort[8,14] they also ensure more accurate drug dosing and longer residence time in mucosa as compared to gel and ointment [13,14,15]. They are formulated to exhibit both systemic and local action. The present research article represents the formulation and evaluation of buccoadhessive film of ropinirole hydrochloride.

MATERIALS AND METHODS

Materials

Analytical pure drug ropinirole hydrochloride was purchased from Jackson Laboratories Pvt. Ltd., (Amritsar, India). Ethanol was purchased from Changshu Yangyuan Chemical, (China). Dichloromethane, ethyl cellulose, hydroxypropylcellulose and propylene glycol were purchased from Loba Chemie Pvt. Ltd., (Mumbai, India). While carbopol 934, isopropyl alcohol, poly vinyl alcohol, potassium dihydrogen phosphate and sodium hydroxide were purchased from Central Drug House (P) Ltd.., (New Delhi, India). All the chemicals used were of analytical grade.

Buccal film preparation

Preparation of dummy polymeric patch with solvent casting method

Propylene glycol (PG), 10% w/v solution was prepared in distilled water which act as plasticizer. Then added different concentrations (1, 3, 5 %w/v) of HPMC and PVA as polymer for six formulations. The resulting casting solution were then deaerated using sonicator and transferred into petri-plates. These are dried in hot air oven at 42°C. The composition of dummy films is shown in table 1 and table 2.

Preparation of drug loaded film

From preliminary physical observations of dummy polymeric patches polymers were selected and combination of these hydrophilic polymers was used along with hydrophobic polymer for the preparation of buccal film of ropinirole hydrochloride and was evaluated for various parameters. Drug loaded buccal films were prepared by solvent casting method. The compositions of different batches of prepared drug loaded films are given in table 3.

Preparation of films containing HPMC, PVA and EC

Formulations F1 to F7 were prepared containing HPMC, PVA and EC of different grades in varying quantities so as to study the effect of different polymers on the drug release from the films. For the preparation of films, solution of weighed quantity of PVA as specified in table 6 was prepared in 3 ml of water. EC was dissolved in 25 ml of ethanol followed by dispersion of HPMC in the same solution. This prepared dispersion was then poured slowly into PVA solution prepared above with continuous stirring. Propylene glycol and drug solution (dissolved in 2 ml water) were then added to the polymer mixture and stirred until a clear solution was obtained. The solution was left undisturbed to obtain bubble free solution. Then it was poured into petriplate and allowed to dry by keeping it at room temperature overnight.

Preparation of films containing carbopol and EC

Formulations F8 to F11 were prepared containing carbopol and EC in different quantities. For the preparation of film, weighed quantity of carbopol and drug were dispersed in 20 ml of dichloromethane (DCM) with continuous stirring for 2 hrs EC was dissolved separately in isopropyl alcohol (IPA) and then EC solution was poured slowly in above prepared dispersion of carbopol and drug with continuous stirring. Propylene glycol was then added to polymer mixture and stirred until a clear solution was obtained. The solution was then left undisturbed to obtain bubble free solution. Then it was poured into petriplate and allowed it to dry at room temperature overnight.

Evaluation of buccal films

Physical appearance and surface texture

The films were observed visually for their appearance parameters such as color, and transparency. The surface texture of films was evaluated by feeling or pressing the films with finger.

Table 1: Dummy polymeric patches of HPMC at different concentration.

Formulations	HPMC %(w/v)	P G (% w/w of polymeric weight)	Water (ml)	Physical characteristics
D1	1	10	30	Transparent, flexible and smooth
D2	3	10	30	Transparent and brittle
D3	5	10	30	Transparent and brittle

Table 2: Dummy polymeric patches of PVA at different concentration.

Formulations	PVA %(w/v)	P G (% w/w of polymeric weight)	Water (ml)	Physical characteristics
D1	1	10	30	Transparent, very smooth and very less strength.
D2	3	10	30	Transparent, flexible and smooth.
D3	5	10	30	Transparent, flexible, smooth and good strength

Table 3: Composition of Buccal films of ropinirole hydrochloride.

Ingredients (mg or ml)	Formulations										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Drug	168	168	168	168	168	168	168	168	168	168	168
EC 15 cps	75	75	75	100	125	-	-	-	-	-	-
EC 50 cps	-	-	-	-	-	200	250	500	500	500	600
HPMC E-15	900	900	-	-	-	-	-	-	-	-	-
HPMC 3000 cps	-	-	500	500	500	500	500	-	-	-	-
PVA	150	200	150	150	150	50	50	-	-	-	-
Carbopol	-	-	-	-	-	-	-	300	400	500	300
PG (% Of w/w	20	20	20	20	20	20	20	30	30	30	30
polymer content) Water	5	5	5	5	5	5	55	-	-	-	-
Ethanol	25	25	25	25	25	25	25	-	-	-	-
DCM	-	-	-	-	-	-	-	20	20	20	20
IPA	-	-	-	-	-	-	-	10	10	10	10

Thickness

The thickness of the patch was measured using micrometer screw gauge at five different positions of the film. The mean was determined along with standard deviation.

Weight variation

Films of area measured 2.26 cm^2 were cut from five different places from the casted film. The weight of such resulted film was taken in digital balance and average weight was calculated and standard deviation was determined.

Folding Endurance

The folding endurance was determined manually for the prepared films by repeatedly folding the film at the same place until it broke down. The number of times the film could be folded at the same place without breaking or cracking gives the value of folding endurance. The mean value of three readings and standard deviation was determined.

Uniformity of drug content

Three films of area measured of 2.26 cm^2 were taken separately in a separate 100 ml beaker. Then added 100 ml of phosphate buffer pH6.8 and continuously stirred in magnetic stirrer. The solution was filtered, diluted and analyzed at 249 nm in a UV spectrophotometer. The content of drug was calculated using standard plot. Average of three readings was calculated and standard deviation was determined.

Swelling index

Swelling index was determined by placing the weighed patches (W1) of 2.26 cm^2 from each formulation in a petriplate containing 50 ml of water. After different time intervals of 5 min, 15 min and 30 min, the film was removed and blotted with filter paper and weight again. The weight of the film was noted. The swelling index was calculated by the following formula.

Swelling index = (W2-W1) / W1 × 100

where, W2 = Wet weight of the film

W1 = Dry weight of the film

Surface pH

The patches were allowed to swell in contact with 5 ml of distilled water for one hour at room temperature and pH was noted down by bringing electrode in contact with the surface of the film, allowing it equilibrate for 1 min. The procedure was performed in triplicate and average with standard deviation was determined.

Tensile strength

Tensile strength of the patch was determined using

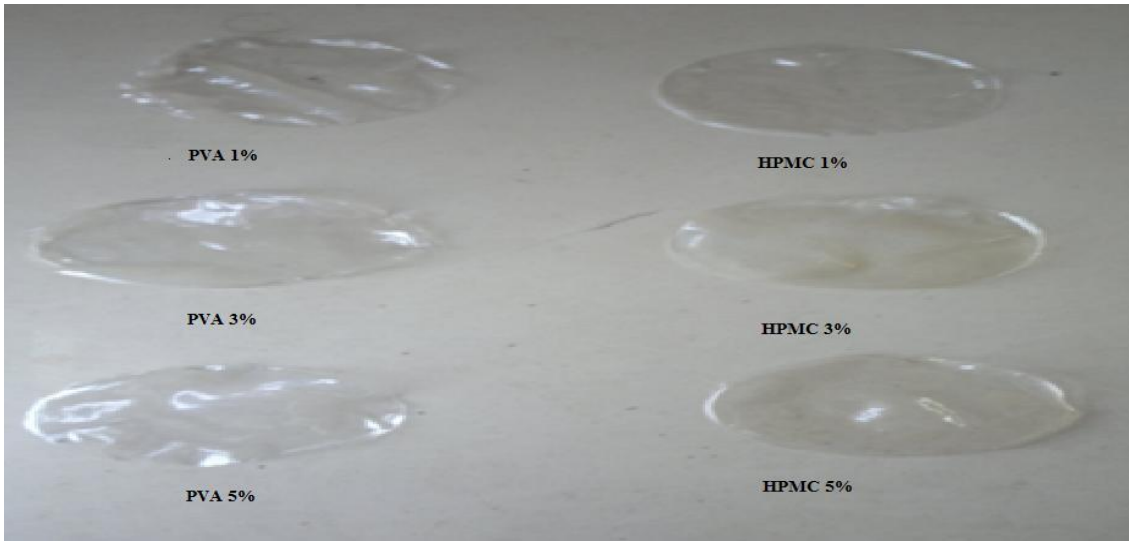

Figure 2: Polymeric patches PVA and HPMC at different concentration.

Table 4: Weight variation of buccal film of ropinirole hydrochloride.

S.No.	Formulation	Weight of 2.26 cm^2 film in mg					Mean ± SD
		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	
1	F1	61	58	61	60	62	60.4 ± 1.51
2	F2	65	63	60	64	62	62.8 ± 1.92
3	F3	48	44	46	47	47	46.4 ± 1.51
4	F4	49	47	45	47	49	47.4 ± 1.67
5	F5	51	50	49	47	50	49.4 ± 1.51
6	F6	43	43	45	43	41	43.0 ± 1.41
7	F7	45	44	45	42	43	43.8 ± 1.30
8	F8	34	36	32	37	35	34.8 ± 1.92
9	F9	36	33	37	35	35	35.2 ± 1.48
10	F10	49	46	49	48	47	47.8 ± 1.30
11	F11	37	39	35	36	37	36.8 ± 1.48

Table 5: Folding endurance of buccal films of ropinirole Hydrochloride

S.No.	Formulations	Folding endurance			Mean ± S.D.
		1	2	3	
1	F1	327	338	318	327.6±10.01
2	F2	352	345	367	354.6±11.23
3	F3	383	392	389	388.0±04.58
4	F4	364	350	372	362.0±11.13
5	F5	356	331	347	344.6±12.66
6	F6	249	254	243	248.6±05.50
7	F7	232	219	225	225.3±06.50
8	F8	172	178	187	179.0±07.54
9	F9	186	198	192	192.0±06.00
10	F10	210	198	201	203.0±06.24
11	F11	153	152	167	157.3±08.38

tensile tester machine - 1.3D, consisting of two loaded cell grips. The upper one is fixed and the lower one movable. The test patch of area 5X3cm^2 was fixed between these cell grips and force was gradually applied till the patch broke. The tensile strength was automatically determined by the machine and was taken directly from the dial reading.

In vitro drug release

In-vitro release studies were carried out using egg membrane as semi permeable membrane. Film having area 2.26cm^2 was placed over egg membrane and tied to open ended cylinder (test tube) and placed in such a way that the film has dipped into receptor compartment (beaker) containing 100 ml of phosphate buffer *(pH 6.8)*. The teflon coated magnetic bead was placed in the beaker and rotated at 100 rpm using magnetic stirrer and the temperature was maintained at 37 ± 0.2^oC. Samples with volume of 5 ml were withdrawn at regular intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12hrs) from

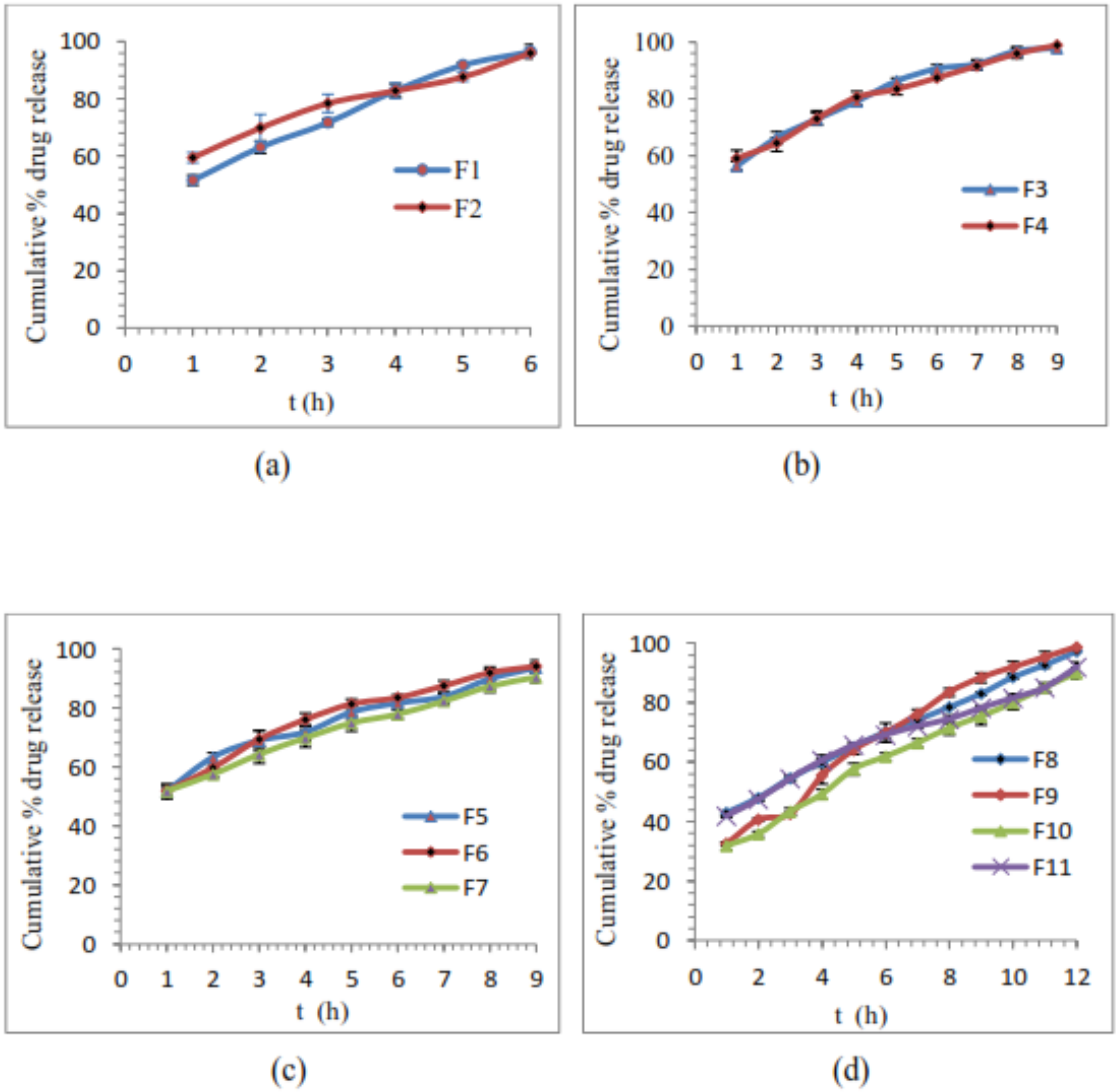

Figure 3: *In vitro* percent drug release versus time plots of (a) F1and F2 (b) F3 and F4 (c) F5, F6 and F7 (d) F8, F9, F10 and F11.

the beaker and replaced the volume with same amount of fresh phosphate buffer to maintain sink conditions throughout the experiment. The collected samples were analyzed by UV spectrophotometer at λ_{max} 249 nm.

RESULT AND DISCUSSION

Formulation of buccal films

Dummy patches were formulated prior to the preparation of drug loaded patches. The composition of dummy patch formulations is shown in table 1 and table 2 and it was observed that different ratios of polymers provide different characteristics like flexibility, brittleness, strength and transparency. On the basis of the observations of the dummy patches, drug loaded patches were prepared in different ratios. The composition of various drug loaded films is given in table 3. However, it was observed that the formulation D1 to F7 were transparent in appearance were as formulation F8 to F11 observed to be opaque due to carbopol content. Surface texture of all the formulation was observed to be smooth and flexible except formulation D2 and D3 as in these HPMC content increased making them brittle.

Evaluation of Buccal film

Weight variation

The prepared films were evaluated for their weight. The results obtained for all the formulations are mentioned in table 4. It has been observed that with increase in polymeric content in the formulation, the corresponding weight was increased.

Film thickness

Film thickness was observed using micrometer screw gauge and the results of determined thickness reveal that as the polymeric amount is increased; there is gradual increase in the thickness. All the film formulation was found to be in the range of 0.13 mm to 0.21 mm.

*Drug content*Drug content was estimated in triplicates for all the formulations using patch area of 2.26 cm^2. It is found that in all the formulations, drug was distributed

Table 6: Analysis of release mechanism of prepared film formulation F10.

Time	CDR	Log CDR	√t	$Wo^{1/3}$-$Wt^{1/3}$	$LogQ_t$-$LogQ_0$
1	1.713998	0.23401	1	0.620371	-0.54414
2	1.927456	0.284984	1.414214	0.572621	-0.49317
3	2.332728	0.367864	1.732051	0.490883	-0.41029
4	2.64927	0.423126	2	0.43342	-0.35502
5	3.101993	0.491641	2.236068	0.358708	-0.28651
6	3.328262	0.522218	2.44949	0.324077	-0.25593
7	3.57452	0.553218	2.645751	0.288126	-0.22493
8	3.843909	0.584773	2.828427	0.250642	-0.19338
9	4.054282	0.607914	3	0.222571	-0.17024
10	4.298464	0.633313	3.162278	0.191181	-0.14484
11	4.579181	0.660788	3.316625	0.15653	-0.11736
12	4.838725	0.684731	3.464102	0.125731	-0.09342

Table 7: Kinetic analysis of film formulation F10.

Kinetic models	In-vitro r^2	
	Slope	r^2
First order	-0.05	0.985
Zero order	0.284	0.992
Higuchi	1.313	0.989
Korsymer peppas	0.419	0.968
Hixson crowel	-0.044	0.969

uniformly and the % drug content was found to be in range of 94.48% ±1.56 to 100.61 % ±1.36.

Surface Ph

The surface pH of buccal film was determined in order to investigate any possibility of mucosal irritation by acidic or alkaline pH. The surface pH of the films was expected to be close to neutral. The results of surface pH were found to be in the range of 6.0 to 6.40 for all the formulations. Results comply with in the range of pH of buccal mucosa and hence these formulations are expected to be non-irritant as far as pH is concerned.

Folding endurance

Folding endurance was done for the prepared films. The patches were folded from 157 to 388 times without breaking. The differences in folding endurance of all the patches are attributed to different polymeric content and their viscosity grades. It has been found that highest folding endurance in formulations are due to highest content and more viscosity grade of HPMC as in case of F3, F4, F2, F5 followed by F1. However, in formulations F1 and F2, increasing the PVA content has also led to increase in folding endurance whereas in formulations F3, F4 and F5, keeping the content and grade of HPMC constant while increasing the EC polymer, decrease in folding endurance is found (yet more than formulations F1 and F2 due to highest viscosity HPMC). In formulations F7 and F8, further decrease in folding endurance is found which is due to increase in higher viscosity grade and content of EC. Carbopol also showed improvement in folding endurance as can be seen from Formulations F8, F9, F10 and F11. Though the improvement was not more than that of HPMC and PVA but it was better than EC.

Swelling index

It was observed that formulations containing HPMC were eroded due to higher water absorption. But the formulations containing carbopol exhibited good swelling behavior. It has also been observed that as the content of carbopol was increased, swelling characteristics also increased. EC leads to decreased swelling index as seen in case of formulation F11 when compared to F8 as both contain same content of carbopol but varying content of EC.

Tensile strength

From tensile strength determination, mechanical properties of the films have been determined. It has been found that formulation F2 contains the better mechanical strength than all other formulations.

In vitro drug release study

All the formulated films were subjected to *in vitro* drug release study. Formulations F1 and F2 showed initial burst release more than (50%) which may be attributed to the concentration of PVA in the formulation. As in F2 as the content of PVA is increased the initial burst release has been increased to 90 % of drug release from the formulation within 6 h. (i.e.no retardation in release). From formulation F3, F4, F5, F6 and F7 change in viscosity grades of HPMC and EC shows no initial retardation but has increased the release up to 9 hrs. As HPMC E-15 and HPMC 3000 cps were not found to be effective in retarding the initial burst release so the polymer HPMC has been replaced with carbopol.

In formulation F8, F9, F10 and F11, EC- 50 cps amount has also been increased so as to retard the release of drug from the patch formulation but on increasing the amount of EC brittleness in the patch was observed. Therefore, to provide sufficient flexibility to the patch propylene glycol content has also been increased. These formulations F8, F9, F10 and F11 contain EC- 50 cps and carbopol 934P in different ratio. Though there was difference in drug release pattern but all the formulations were able to retard the drug release up to 12 hrs. It has also been observed that with increase in carbopol content initial burst decreased (Fig 3).

Formulation F10 was found to be the best as there is desired pattern of release i.e. sustained release has been found. This may attribute to increase amount of polymer in the formulation (500mg EC-50 cps: 500mg carbopol934P) (1:1). Hence, it can be concluded that use

of carbopol lead to initial retardation however EC also contributes to provide prolonged release but not initial burst release as seen in case of F11. Hence, further kinetic models were applied on the drug release of formulation F10 so as to analyze its release mechanism (Table 6 and 7).

CONCLUSION

Buccal films of ropinirole hydrochloride were prepared using various polymers (HPMC, EC, PVA and carbopol) by solvent casting method using propylene glycol as plasticizer. All the formulations were evaluated for various parameter such as appearance, surface texture, weight uniformity, thickness, folding endurance, surface pH, drug content and swelling index.

All the films were smooth and flexible with transparent and opaque appearance. They were uniform in their weight and thickness and almost uniform in their drug content with low SD value. The pH values were found to be 6.0 to 6.40 that comply with the range of buccal mucosa. Folding endurance of all the patches attributes to different polymeric content, and their viscosity grades. Formulation containing carbopol exhibit good swelling behavior were as formulation containing HPMC get eroded due to high water absorption. Formulation containing PVA shows higher tensile strength due to their more elastic behavior.

All the formulations were subjected to in vitro drug release study which were carried out using egg membrane as semi permeable membrane. Formulation F10 was found to be the best and it was subjected to various kinetic models. The formulation F10 follows zero order kinetic that conclude that formulation shows sustained drug release.

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