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Nanoparticles loaded sublingual film as an Effective Treatment of Chemotherapy Induced Nausea and Vomiting

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Abstract: The aim of present study was formulation and evaluation of Mucoadhesive sublingual film containing nanoparticles of poorly water soluble drug to get quick disintegration for rapid release and onset of action in case of nausea and vomiting produced by chemotherapy, migrane, headache, food poisoning and viral infections. To improve the solubility of Domperidone, nanosuspension was prepared by using high speed homogenizer. HPMC E 5 and SDS were used to stabilize the nanosuspension. HPMC E 5 is a key ingredient in formulation of film which rapidly disintegrate in presence of water or saliva. Formulations weer prepared by varying the concentaration of polymer and plasticizer. Mucoadhesive polymer such as carbopol 934P was used to in the film for mucoadhesion of film to sublingual mucosa. Nanosuspensions were evaluated for parameters like Particle size, PDI and Zeta potential. Films were evaluated for parameters like drug content, tensile strength, in-vitro drug release, folding endurance, surface pH, taste, thickness, disintegration time, ex vivo Mucoadhesion time, ex vivo permeation study and drug excipients compatibility study. In this study, the release profile depends on the concentration of HPMC E 5. A 3^2 Factorial study was applied to check the effect of varying concentration of HPMC E 5 and propylene glycol on dependent variables i.e disintegration time, % in vitro drug release and tensile strength. Regression analysis and analysis of variance were performed for dependant variables. Study demonstrates dissolution rate increased in film containing the nanoparticles of drug and quick disintegrating film of Domperidone can efficiently be formulated.
Keywords: Nanoparticles loaded sublingual film, Chemotherapy, Nausea and Vomiting.

Introduction

Domperidone is a specific dopamine receptors(D2 and D3) blocker and is widely used to treat emesis. It causes dopamine receptor blockage both at the chemoreceptor trigger zone and at the gatric level. It shows low oral bioavailability (10-15%) due to higher first pass metabolism in gut wall and liver. In view of high first pass metabolism and short plasma half life it is an ideal candidate for rapid disintegrating drug delivery system.[1,2]

The drug is available in tablet dosage form and is practically insoluble in water, achieving sufficient bioavailability of this drug is difficult.[2]

The BCS is a scientific background for classifying drug substances depending on their aqueous solubility and the intestinal permeability. When combined with the dissolution of the drug product, the BCS takes in to account 3 main factors that direct the rate and extent of drug absorption from immediate-release

solid oral dosage form: dissolution, solubility, and the intestinal permeability. According to the BCS, drugs substances are classified as follows:[3]

Class I: high solubility – high permeability
Class II: Low solubility – High permeability
ClassIII: High solubility – Low permeability
Class IV: Low solubility - low Permeability

A nano suspension is a submicrone colloidal dispersion stabilized using surfactants. The particle size distribution in nanosuspesion is usually less then one microne with an average particle size ranging between 200 and 600 nm. In nanosuspension drug is kept in the required crystalline state with reduced particle size, principal to an increased dissolution rate and hence enhanced bioavailability. An increased in the dissolution rate of micronized particles (particle size < 10 μm) is associated to an increase in the surface area and dissolution rate. Nanosized particles enhances solubility rate and saturation solubility because of the vapor pressure effect. [3,4,5]

Thin film drug delivery is a process of transporting the drug to systemic circulation via thin film that dissolves when comes in contact with liquid, dissolves with in 1 min when placed in the mouth without drinking water or chewing. Thin film's capacity to dissolve rapidly without water provides substitute to patient with swallowing syndromes and to patients having chemotherapy induced nausea. Fast dissolving films are attainment interest as an alternative to fast dissolving tablets to definitely eliminate patient's fear of chocking and overcome weakness. The films should be stable to moisture, facilating the handling, have to flexible and exhibit a suitable tensile strength and do not stick to the packaging material and fingers.[6]

The term bioadhesion denotes to any bond formed between two biological surfaces or bond between a biological and artificial surface. In case of bio-adhesive drug delivery, the term bio-adhesion is used to define the adhesion between polymers, either synthetic or natural and soft tissue or the gastrointestinal mucosa. bioadhesion is term which broadly includes adhesive interactions with any biological or biologically derived substance, and Mucoadhesion is used when the bond is formed with a mucosal surface.[7]

Experimental Work

Material and method

Domperidone was received as gift sample from torrent research center, Bhat, Gandhiangar, Gujarat. HPMC E 5, propelyne glycol, aspartame and SDS were procured from lobachamie laboratories, vadodara, India. Carbopol 934p was obtained from Qualikems fine chem.. Pvt. Ltd., vadodara, India.

Preparation of film

Polymeric solution of HPMC E 5 of different concentration shown in table 1, were prepared in 10ml of distilled water with constant stirring for 15 mins. 20 ml of polymeric solution were divided into two parts 10 ml each. In first part Drug and SLS were dispersed. In second part different concentration of plasticizer according to table 1 3and carbopol 934P and other excipients were dissolved. Both the solution were thoroughly mixed and homogenized by using High speed homogenizer at 12000 RPM for 15 minute. Size of particle, present in liquid was measured by Malvern Zetasizer. Processed suspension casted into petridish and dried at room temperature for 48 hours.

Calibration curve of Domperidone in simulated salivary fluid pH 6.8:[8]

Prepared stock solution (100 μg/ml) was further diluted to get concentration of domperidone in the range of 2-18μg/ml with pH-6.8 simulated salivary fluid. Absorbance of each solution was measured using shimadzu 1800 UV-Visible double beam spectrophotometer against simulated salivary fluid as a blank (285nm). The standard curve was generated for entire range of concentrations. Repeated three time and based on average absorbance; the equation for the best line was generated.

Drug-Excipient Compatibility studies:

Fourier transform infrared spectroscopy was carried out for checking the interaction were present between drug and polymer. Samples were prepared by potassium bromide disk method (3 mg sample in 297 mg KBr). Powders were triturated in a small size glass mortar and pestle until the powder mixture was fine and uniform. Pure KBr was used as background and for base]line correction. Samples were placed in sample holder. Afterward, the samples

Was transferred to sampling compartment, were scanned in the region of 400-400cm^{-} using buker FTIR spectrometer.

Formulation table

Table 1: formulation of drug and Expients in film

Ingredient	Batch								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Domperidone (mg)	120	120	120	120	120	120	120	120	120
HPMC E 5 (mg)	200	250	300	200	250	300	200	250	300
Propylene Glycol (% w/w)	15	15	15	20	20	20	25	25	25
Aspartame (mg)	40	40	40	40	40	40	40	40	40
SDS (mg)	10	10	10	10	10	10	10	10	10
Carbopol (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Water (ml)	20	20	20	20	20	20	20	20	20

Evaluation

Evaluation of Nanosuspension

Particle Size & zeta Potential [9]

Particle size of different formulation prepared was measured with help of Malvern zeta sizer. Values of average particle size diameter and poly dispersity index(PDI) of nano suspension were measured. Zeta potentials of formulations were measuredny at 25 ±0.5^{0}C.

Evaluation of Dosage form

Weight variation [10]

Film was cut in to five different strips from casted petridish. Weight of each film was taken and variation was calculated.

Film thickness[10]

The thickness of 3 film was measured by screw gauge micrometer at different position of film and average thickness was calculated.

Folding endurance[11]

A film of 2 x 2 cm^2 was repeatedly folded and unfolded at the same place till it brakes. The number of times, the film could be folded at same place, without breaking was recorded as the value of folding endurance. This gives an indication of brittleness of the film.

Surface pH[10]

The film to be tested was placed in a petridish; 1 ml of distilled water was added and kept for 30 seconds. The pH was noted after by electrode of the pH meter allowing contact time of 1 min. the average of three measurements for each formulation was carried out.

Disintegration time[12]

In-vitro Disintegration tine was determined visually in petridish containing 25 ml of simulated salivary fluid pH 6.8.

Drug Content

Determined by dissolving one film of dimension of 2 x 2 cm^2 in 100 ml of pH 6.8 simulated salivary fluid for 30 minutes. From this, 1 ml was diluted to 10 ml and absorbance was measured at 285.0 nm using UV spectrophotometer.

In vitro dissolution study[10]

Dissolution profile of formulation was carried out using USP type II (paddle apparatus) with 300ml of pH 6.8 simulated salivary fluid as dissolution medium maintained at 37± 0.5 °C. Dissolution medium was stirres at 50 rpm. Samples were withdrawn at every 30 second interval, replacing the same amount with fresh medium. Absorbance was determined by UV spectrophotometer at 285.00 nm.

***EX vivo* Mucoadhesion time**[11]

Determined by application of film on freshly cut porcine buccal mucosa. The porcine tissues were fixed on the internal side of the beaker with glue. Film was wetted with 50 µl of simulated saliva fluid and was pasted to the porceine buccal tissue by applying a light force with fingertip for 20 seconds.

The beaker was filled with 200 ml simulated salivary fluid and kept at 37 °C. after 2 min, stirring rate was set at 250 rpm to simulate the buccal cavity environment and during the test

The time taken for film to completely erode or detect from the mucosa was considered as the *ex vivo* Mucoadhesion time.

Ex-vivo permeation studies[11,13,14]

Ex vivo permeation studies through porcine oral mucosa (ventral surface of tongue) was carried out using the Franz diffusion cell. The buccal mucosa was excised and trimmed evenly from the sides, washed in SSF of pH 6.8 and used immediately. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 25 ml of SSF of pH 6.8 which was maintained at 37± 0.2^0C and hydrodynamics were maintained using magnetic stirrer. One film of dimension 2 cm × 2 cm was previously moistened with a few drops of pH 6.8 phosphate buffer and placed in donor compartment. The donor compartment was filled with 1 ml of pH 6.8 SSF. 1 ml samples from receptor compartment were withdrawn at suitable time interval which was then replaced with 1 ml of pH 6.8 phosphate buffer. The percentage of

domperidone permeated was determined by measuring the absorbance in UV-Visible spectrophotometer at (λ_{max}) 285 nm.

Tensile strength[11]

Tensile testing was conducted using a texture analyzer. The film was cut into 60 × 20 mm strips. Tensile tests were performed according to ASTM International Test Method for Thin Plastic Sheeting on the texture analyzer. Initial grip separation was 20 mm and crosshead speed was 1 inch/min. The test was considered concluded when the film breaks. Tensile strength, was computed with help of load require to break the film and cross sectional area to evaluate tensile properties of the films. Tensile strength (TS) Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area.

Tensile Strength = Force at break (N)/ Cross sectional area (mm^2)

Stability Study

The stability study was carried out on the optimized formulation F_4 over the period of one month. The F_4 formulation was sealed in aluminum foil and kept in humidity chamber maintained at 40 ± 2°C / 75 ± 5% RH for one month. At the end of studies, a sample was analyzed for the drug content, in vitro drug release, disintegration time.

Result

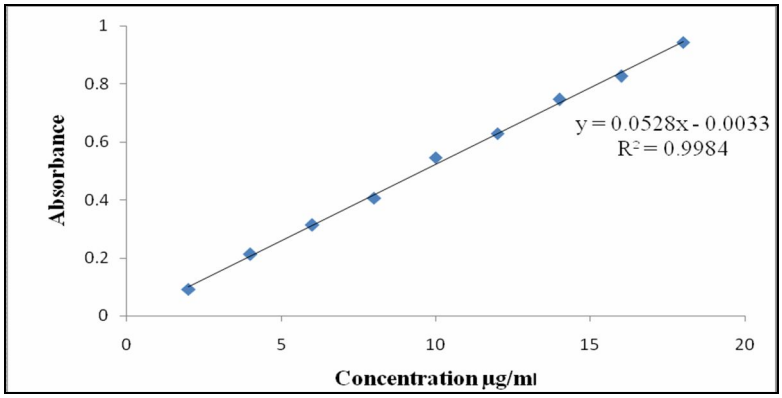

Figure 1: Calibration curve of Domperidone in pH 6.8 Simulated Salivary Fluid

Drug-excipient Compatibility Studies:

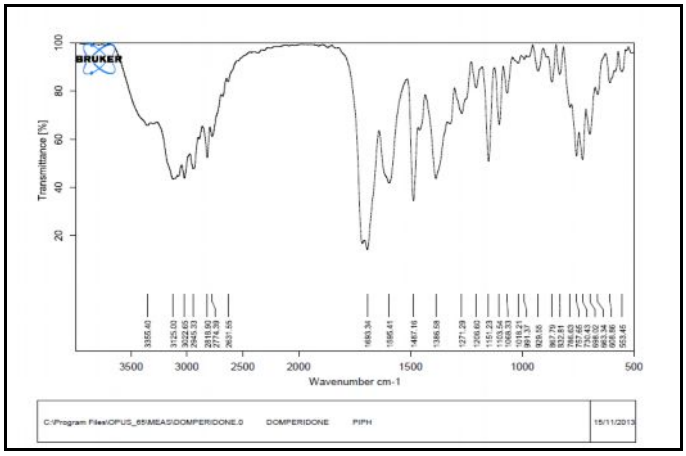

Figure 2: FT-IR spectrum of pure drug

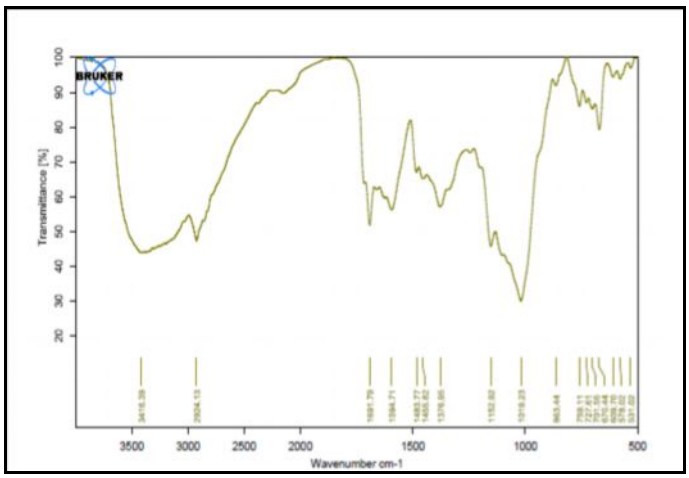

Figure 3: FT-IR spectrum of Physical Mixture

Results of batch (F1 to F9)

Mechanical properties (batch F1 to F9)

Table 2 Mechanical properties of batch (F1 to F9)

Batch	Thickness (mm)	Weight (mg)	Tensile strength N/mm^2	Folding Endurance
F1	0.06±0.005	28.66±1.69	19.08	102.33±2.49
F2	0.07±0.003	34±0.81	19.72	105±1.63
F3	0.07±0.006	40.33±1.24	20.32	111±0.81
F4	0.06±0.006	29±0.81	21.62	119±0.81
F5	0.07±0.004	34.33±1.24	22.34	123±1.63
F6	0.07±0.005	42±0.81	23.21	129.55±1.69
F7	0.06±0.005	30±0.81	23.89	131±2.05
F8	0.07±0.001	34.66±1.24	24.09	133±1.41
F9	0.08±0.002	42.33±1.24	24.89	134.88±2.86

Mean ± S.D, n=3

Physico-chemical characterization (batch F1 to F9)

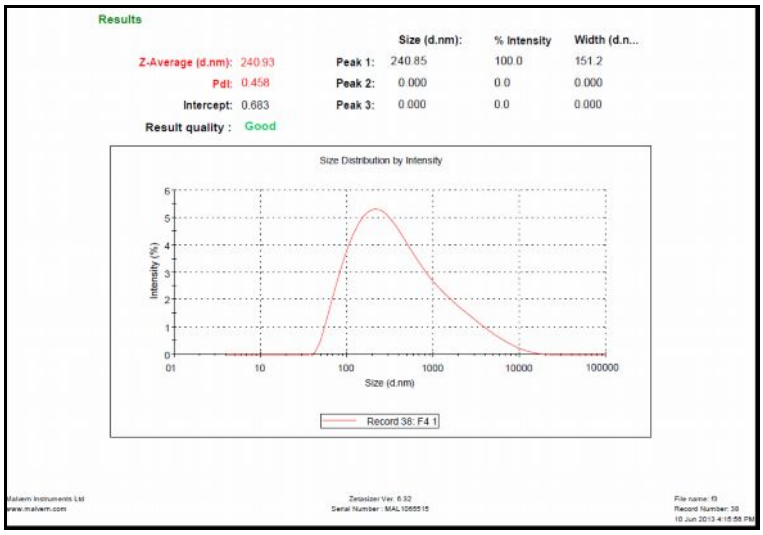

Figure 4: Particle size distribution of drug nanoparticles by Malvern Analyzer

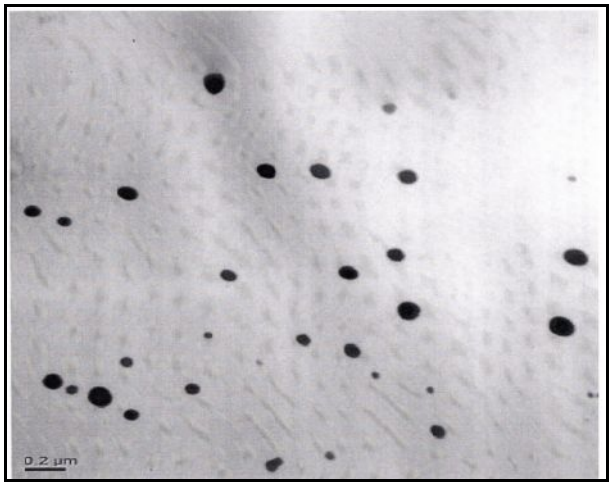

Figure 5: SEM image of the drug particle

Table 3 Physicochemical Properties of batch (F1 to F9)

Batch	Particle size (nm)	Surface pH	Disintegration Time (sec)	Drug content (%)
F1	326.5	7.18±0.01	12±0.97	93.17±1.13
F2	211.5	7.26±0.01	24±0.89	94.15±0.86
F3	346.5	7.38±0.02	35.99±0.10	94.28±0.96
F4	241.6	7.48±0.01	16±0.10	95.98±1.56
F5	281.5	7.54±0.01	28±0.71	96.18±0.45
F6	409.11	7.34±0.01	42±0.12	96.57±0.21
F7	431.87	7.54±0.01	18±0.96	93.99±2.18
F8	267.56	7.24±0.02	32.1±0.05	94.68±0.97
F9	509.89	7.37±0.01	44.89±0.98	96.58±1.53

Mean ± S.D, n=3

***% In-vitro* drug release of factorial batch F1 to F5**

Table 4: *% In-vitro* drug release of batch F1 to F5

Time(sec)	f1	f2	f3	f4	f5
0	0	0	0	0	0
30	30.118	20.403	15.915	24.205	14.82
60	42.98	34.675	31.45	37.92	26.731
90	55.937	43.957	39.315	48.395	32.498
120	64.312	54.015	46.985	57.875	42.024
150	71.058	62.865	53.973	66.257	48.92
180	74.012	67.845	64.954	72.865	59.245
210	76.124	73.101	70.254	77.254	65.487
240	77.624	75.976	73.883	79.995	71.523
270	81.114	79.054	76.955	81.995	76.341
300	81.918	80.741	78.712	83.897	78.995

Mean ± S.D, n=3

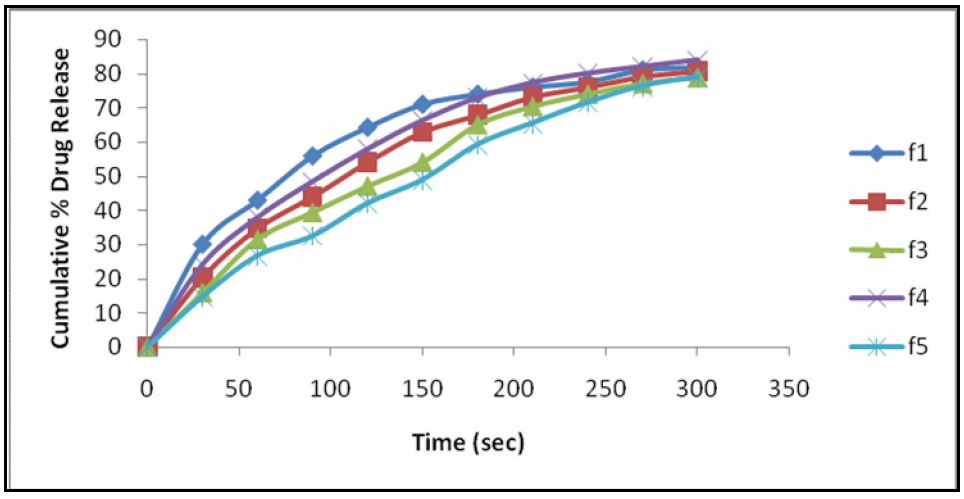

Figure 6: cumulative % drug release of batch F1 to F5

Table 5 : *% In-vitro* drug release of batch F6 to F9

Time(sec)	f6	f7	f8	f9
0	0	0	0	0
30	10.986	19.522	10.354	6.754
60	27.625	31.543	21.874	19.647
90	36.574	43.654	29.354	27.745
120	45.998	54.575	40.841	34.254
150	52.658	60.685	49.852	44.687
180	58.855	67.758	57.147	51.457
210	66.357	72.14	65.975	62.957
240	74.947	75.454	71.124	68.245
270	76.981	77.987	75.347	73.124
300	77.005	79.657	77.987	75.957

Mean ± S.D, n=3

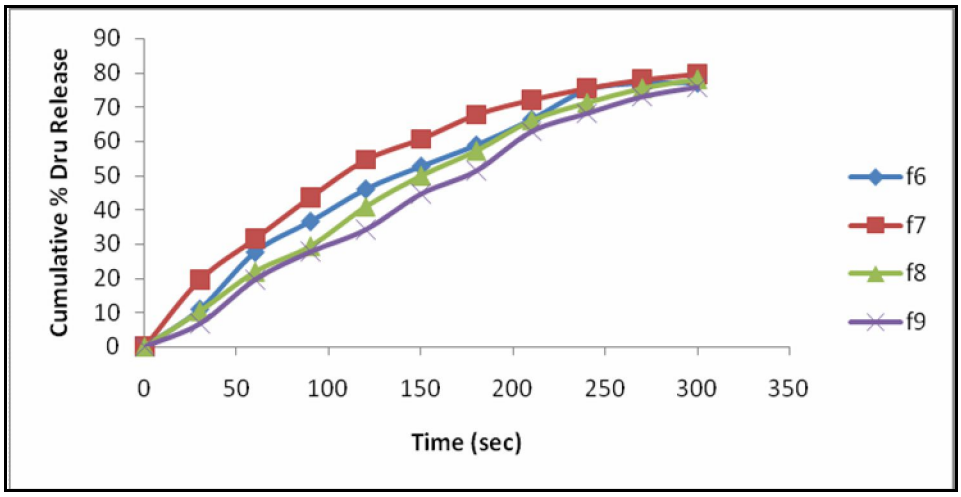

Figure 7: Cumulative % drug release of batch F6 to F8

Ex vivo Permeation study of optimized batch and Film without high speed homogenization

Table 6: Ex vivo Permeation study of batch N1 and N2

Time (min)	Film Containing Nanoparticles (N1)	Film without high speed homogenization (N2)
	% Drug permeated	
0	0	0
2	4.53	1.61
5	14.42	4.3
10	29.32	8.929
15	43.73	12.94
20	58.31	15.41
25	67.64	18.78
30	74.64	21.5

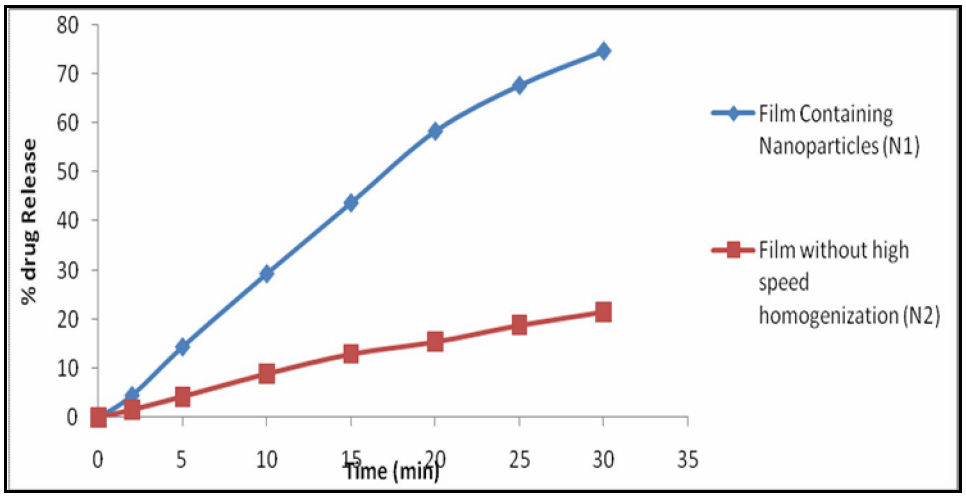

Figure 8: Ex vivo Permeation of batch N1 and N2

Table 7: Disintegration Time, %Drug released and % Drug content of an optimized formulation -+after one month at 40°C±2°C and 75%±5% RH

Parameters	Before one month	After one month
Disintegration Time (Seconds)	14±0.81	15± 0.15
% Drug released	85.847±0.46	84.357± 0.53
% Drug Content	96.78±0.24	95.14± 0.72

Mean ± SD; n=3

Discussion

Calibration curve of Domperidone in pH 6.8 Simulated Salivary Fluid

Calibration curve of Domperidone was prepared in Simulated salivary fluid pH 6.8 at λ_{max} 285 nm. Regression value (R^2) was found to be 0.998 (Figure 1), which indicates standard solution follows Lambert-beer's law in the range of 2-18 µg/ml.

Drug-excipient Compatibility Studies:

All the characteristic peaks of groups of pure drug Domperidone were appear in FTIR spectrum. As can be clearly seen from the FTIR spectra(Figure 1 & 2)., Domperidone shows characteristic peaks, group's peaks were also appear in physical mixture of Domperidone with excipients. So, FTIR gave conformation about their purity and showed no interaction between drug and polymer.

Weight & Thickness:

Weight of film & the thickness was in the range of 28.66±1.69 to 42.33±1.24 mg & 0.06±0.005 to 0.08±0.002 mm respectively. As the polymer concentration increased both the weight & thickness of film was also increased.

Tensile strength:

Tensile strength of film was in the range of 19.02 to 24.92 N/mm^2. As the plasicizer concentration increase tensile strength of film also increases.

Folding Endurance:

Folding endurance was measured by folding the film at the same place repeatedly until a visible crack is observed. This gives an indication of brittleness of the film. As the polymer concentration and plasticizer concentration increases folding endurance increases.

Particle size:

Particle size of nano suspension was measured by using Malvern zeta sizer, before casting the film, particle size of the nanosuspension was found to be in the range of 211.5 – 509.89 nm.

Surface pH

Surface pH of the film was found to be in the range 7.16±0.01to 7.35±0.01 pH, which was close to the neutral pH, which indicate that films may have less potential to irritate the sublingual mucosa and hence, more acceptable by the patient.

Disintegration Time:

Disintegration time was within range of 13±0.81 to 45.66±1.24 seconds in case of Domperidone film. All film were dissolved within a minute. As the polymer concentration increased disintegration time increased.

***Ex vivo* mucoadhesion time:**

Ex vivo mucoadhesive time was shown good for all batches. It should found in the range of 51 to 102 seconds.

Drug content (%):

Drug content for all the formulation was found to be good, within the range of 92.53±0.86 to 96.59±1.56. It can be considered that the drug was distributed uniformly throughout the film.

% In-vitro drug release of batch F1 to F9

% In vitro Drug release was performed in pH 6.8 Simulated Salivary Fluid, which shows good result. Release of factorial batches (F1 to F9) were found to be in the range 76.808± 0.72 to 84.754± 0.46. From results we conclude that drug release rate decrease as the polymer concentration increases. F4 batch shows highest % drug release compared to all batch.

Ex vivo Permeation study of optimized batch and Film without high speed homogenization

Ex vivo Permeation study of optimized batch and Film without high speed homogenization was performed. % drug permeation (through porcine sublingual mucosa) of optimized batch and Film without high speed homogenization was found to be 74.65± 0.68 and 22.50± 1.42 respectively. Due to nanoparticles of drug present in film, dissolution rate increase and permeation of drug observed was more compared to film without high speed homogenization.

The result of Stability studies indicated that, no significant changes were observed with respect to Disintegration time, % Drug released and % Drug content before and after one month. This indicated that, optimized batch was stable.

Conclusion

The Mucoadhesive sublingual film of Domperidone prepared by the solvent casting method showed good mechanical properties and satisfactory release parameters. The prepared film contains nanoparticle and showed improved dissolution rate compared to film containing drug without homogenization. The Multiple regression analysis of the result led to equation that describe adequate influence of the selected variable of concentration of HPMC E5 and concentration of propylene glycol on the response under study. Bitter taste of drug was masked with the help of sweetener aspartame. Film showed mucoadhesive properties due to Carbopol 934p. Film of Domperidone shows good release and patient acceptable physical characteristic.

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