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Research Article

Formulation Development and Evaluation of Duloxetine Hydrochloride Mucoadhesive Patch System for Oral Drug Delivery

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ABSTRACT
Design, develop and evaluate gastrointestinal mucoadhesive patch system (GIMAPS) of an anti – depressant for oral drug delivery. With the objective of using innovative approach to administer Duloxetine hydrochloride (DLX), formulations were designed as GIMAPS by ensuring drug protection in acidic environment and giving a controlled unidirectional release. Gastro-Intestinal Muco-Adhesive Patch System (GIMAPS) is an approach for inducing greater levels of absorption and stability at the intestinal epithelium and administered as oral drug delivery system. This method involves the useof millimetersize mucoadhesive patches that adhere to the intestinal wall and direct solute diffusion towards the wall. It comprises layers of thin, flexible multi-membranes like an impermeable backing – water insoluble polymer; a drug reservoir; a rate controlling membrane and an adhesive. Formulation batches F7 and F10 showed tensile strength of 7-8Nmm^2. Swelling indexofbatchF7andF10after30minswas12.52and14.28.Drugreleasefrombatch F7 and F10 after 8hrs was 76.39% and 74.82% respectively. Both the batches followed zero–order kinetics with co-relation co-efficient r^2 – 0.9566 and 0.9789 respectively. Permeation study from batch F7 and F10 showed drug permeated about 59.85% and 60.12% respectively. Thus it can be claimed that the GIMAPS formulations of batch F7 and F10 are stable, efficacious and capable of releasing DLX for a period of 8 hrs.

KEYWORDS: GIMAPS, Mucoadhesive, FTIR-ATR, hydrophobic polymer, Thickness Uniformity

1. INTRODUCT

In-order to develop new methods of administration for an existing drug, it often costs significantly less, which results[1] in improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. Hence, pharmaceutical companies have to strive hard under constant stress to maximize the full prospective of a drug candidate at an early stage of its life cycle [2]. This rationale can be achieved by incorporating the drug into various drug delivery systems. This can lead to extended patent life and convenient dosage forms that surmount previously presented administration problems. Pharmaceutical research is leading towards innovations in the area of drug delivery at much faster pace as compared to the last two decades[3].

Mucoadhesive drug delivery is gaining a lot of demand due to its increased potential in delivery of drugs through systemic circulation. It allows drugs to circumvent some of the body's natural defense mechanisms. In trans mucosal delivery of therapeutic agents, membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism [4].

In recent years many such mucoadhesive drug delivery systems have been developed for oral, buccal, sublingual, nasal, intestinal, rectal and vaginal routes for both systemic and local effects[5]. Mucoadhesive drug delivery system prolongs the residence time of the dosage form at the site of application (gastric or small intestine) or absorption and facilitate an intimate contact of the dosage form with the underline Absorption surface and thus contribute to improved and/or better therapeutic performance of the drug[6].

Present work is on Gastrointestinal Muco-Adhesive Patch System, also known as GIMAPS. This is an approach for inducing greater levels of absorption and stability at the intestinal epithelium and administered as oral drug delivery system[7]. This method involves the use of millimeter size mucoadhesive patches that adhere to the intestinal wall and direct solute diffusion towards the wall similar to that observed in the case of a transdermal patch[8]. Patch system comprise layers of thin,

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flexible membranes: An impermeable backing – water insoluble polymer; a drug reservoir; a rate controlling membrane and an adhesive layer. Gastrointestinal mucoadhesive patch systems (GIMAPS) have three key attributes like bioadhesive properties for retention of the dosage form, controlled and unidirectional release drug release towards the intestinal epithelium and drug protection. Provides protection from gastrointestinal[9]l degradative processes combined with site specific delivery to absorptive regions of the intestinal tract is purported to yield high local concentrations of the drug in close proximity with epithelial cell layer and hence transport across the barrier of the intestinal membrane. The present research work emphasizes on the formulation development using bioadhesive polymers, to improve the bio availability along with minimal variation in the therapeutic response[10].

MATERIAL AND METHOD

Solubility

For qualitative solubility study, approximately 10mg of the drug was dispersed in 10ml of different solvents like water, methanol, acetonitrile, acetone, chloroform, ethyl acetate, dimethyl formamide followed by sonication for one minute. Dispersion was observed for clarity of the mixture.

FTIR-ATR Study

Prior to the study, the drug DLX, and potassium bromide were dried for 3hrs at 110°C[11]. Mixture of the drug and potassium bromide were taken in the ratio of 1:150 and were triturate dinamortar using a pestle for uniform dispersion of DLX. Mixture was then pelletized using IR compression machine to develop at hinuni form and transparent pellet. The identity of the sample was confirmed by recording the scan in the range from 4000cm-1- 400cm-1 in FTIR-ATR spectrophotometer [12].

X-Ray Diffraction

To check and confirm presence/absence of any polymorphic forms of the given drug DLX, XRD was performed. X-ray diffraction pattern study was done using Panalytical Xpert PRO XRD. Powder X-Ray patterns are recorded using zero background holder with silicon substrate. Conditions maintained during the scan were Cu target 1.5405Å wavelength 40KV/30mA with secondary monochromator and Xccelerator detector[13].

Differential Scanning Calorimetry

To understand the thermal behavior of the drug, DSC was performed and its melting point was determined.2-3mg of sample was placed in a standard aluminium crucible fitted with a perforated lid for scanning. An empty pan was used as a reference. The samples were heatedatarateof10°C/minoveratemperaturerangeof30–200°Cundernitrogen atmosphere[14].

UV spectroscopy

DLX was accurately weighed and dissolved in methanol to prepare stock solution of 1000µg/ml. This solution was further diluted with methanol to obtain 10µg/ml concentration. Similarly, dilute solutions were also prepared with distilled water to obtain 10µg/ml concentration[15]. By using UV spectrophotometer, all sample solutions were scanned against respective e blank solution sin the range of 200 to 400nm to find absorption maximum (λ_{max}). Optimization trials for GIMAPS were performed as Here Ethyl Cellulose and Eudragit RSPO were chosen in the trials with different mucoadhesive polymers.

Final procedure and formula

Final formula remained the same, but the procedure was modified. Mucoadhesive polymer was added to the drug layer solution during the process. Final patches were packed in aluminum foil and stored in desiccators to maintain the integrity and elasticity of the patches[16]. These formulations were further subjected to various evaluations. After the tensile strength evaluation of the above said batch ofFP1 – FP15, slight modification were done on the final compositions of batches, coded F6-F20. Here the mucoadhesive polymer and drug layer polymer are taken in proper proportion as described in table 1

Table 1: Ratio of mucoadhesive and HPMC polymers in percentage

Formulation code	Ratio of mucoadhesive and HPMC polymers in percentage					
	Carbopol 971PNF	Carbopol 974P	Polycarbophil	Sodium CMC	HPC	HPMC-5cps
F6	25	-	-	-	-	75
F7	50	-	-	-	-	50
F8	75	-	-	-	-	25
F9	-	25	-	-	-	75
F10	-	50	-	-	-	50
F11	-	75	-	-	-	25
F12	-	-	25	-	-	75
F13	-	-	50	-	-	50
F14	-	-	75	-	-	25
F15	-	-	-	25	-	75
F16	-	-	-	50	-	50
F17	-	-	-	75	-	25
F18	-	-	-	-	25	75
F19	-	-	-	-	50	50
F20	-	-	-	-	75	25

Preparation of enteric coated capsule shell

Capsule size of# 0 and #2 were taken for *in-vitro* and *in-vivo* studies respectively. For enteric coating of capsule, 10%w/v solution of Eudragit L100 in40%w/v of plasticizer to that of dry polymer weight was taken in acetone as solvent. Capsules were enteric coated manually by dip method. Here possible care was taken to obtain a uniform coating. After the completion of coating it was left to air dry at room temperature[17].

Physical evaluations

Prepared finalized batches of GIMAPS from batch F6 to batch F20 were visually evaluated for physical characteristics like color, odor, presence of air bubbles, clarity, flexibility etc. Film folding endurance and flatness were also determined[18].

Folding Endurance

Film folding endurance was determined on GIMAPS batches from F6 to batchF20 by repeatedly folding the patches at the same place until any cracks or breaks were visible. The number of times the film could be folded without breaking/cracking gave the value of folding endurance. Six randomly selected patches of each formulation were tested[19].

Flatness

Longitudinal strips from six randomly selected medicated films of each formulation were cutout from GIMAPS batch F6 to batch F20.The length of each strip and variations in length due to non-uniformity of flatness were measured. Flatness was calculated by measuring the constriction of the strips. 0% constriction was considered to be 100% flatness.

Moisture Content

The moisture content of the films was determined by loss on drying. Films were dried at 40°C until constant weight was achieved.

Thickness Uniformity

For thickness uniformity of GIMAPS, patches were measured by using vernier calipers. The measurements were performed on 10 different randomly selected patches from each batch and thickness measured at six different points in order to evaluate the statistical difference, if any. The homogeneity of film formulations in thickness is evaluated by these measurements. After measurements at six different points of ten randomly selected patches of the batch, the results were expressed in terms of mean ± standard deviations[20].

Weight Uniformity

The patches were subjected to weight variation by individually weighing ten randomly selected patches from each batch.4 digits–Shimadzu balance was used for this determination.

Drug content uniformity

The patch of $4cm^2$ area was dissolved in 50ml of phosphate buffer pH 6.8 and kept in orbital shakerfor24hrs at 50rpm at room temperature. After24hrs of shaking, the solution was suitably diluted, and was measured for UV absorbance at 218nm against phosphate buffer pH 6.8 as blank. For each formulation three films were assayed individually. From each film batches, three GIMAPS were selected randomly and assayed by UV spectroscopy method.

Swelling studies:

Swelling Index

Pieces of GIMAPS about 2.0cm*2.0cm ($4cm^2$) were weighed (W_0) (Shimadzu AUX 220) and immersed in 5.0ml of simulated intestinal fluid buffer, pH 6.8 for 30min. After every five minutes time interval, the weight of swollen film was recorded for the experimental time period of 30min. After removal of excess water, the hydrated films were re-weighed (W_t). The procedure was repeated 6 times for each system. Results are obtained using in equation 4.7 indicating the amount of swelling relative to the original weight[21]

Swelling Index=$(W_t-W_0)/W_0$

Where,

W_0 is the weight of film at time zero and W_t is the weight of the film at time t.

Surface pH

Surface pH of the patches was determined by the method described by Botten berg et al. The patches were allowed to swell by keeping them in contact with 0.5ml of double distilled water for 1hr in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1min.

WATER VAPOURTRANSMISSION

The water vapour transmission is defined as the quantity of moisture transmitted through unit area of a patch in unit time. The water vapour transmission data through GIMAPS are important in knowing the permeation characteristics. Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried to constant weight in an oven. About 1gm of fused calcium chloride as a dessicant was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape[22]. These pre-weighed vials were stored in a humidity chamber at an RH of 80% with the temperature set to 30ºC for a period of 24hrs. The weight gain was determined every hour up to a period of 12hrs. The water vapour transmission was calculated using the equation

Rate= WL/S
Where,
S is exposed surface area of the patch.

TENSILESTRENGTHEVALUATION

The polymer films were cut into narrow strips with a width of 25mm and 30mmin length. The films were placed between the higher and the lower grip of a universal testing machine (Lloyds LF PLUS) mounted on a test stand, aligning the long axis of the specimen and the grip with an imaginary line by joining the points of attachment of the grips to the machine. The two grips were kept at a distance of 10mm in a same plan, and the hand wheel attached to the lower grip was rotated gradually until the film broke. Load at the moment of break was recorded and tensile strength was calculated using the equation [23]

Tensile strength (σ)=Force or Load (F) / MA

Where,

F is the maximum load in Newton and MA is minimum cross- sectional area of the film specimen in square millimeter. Displacement and force of detachment were recorded. Based on the force vs. time curve, peak force (F_{max}, g) and area of work (AUC, g s) were obtained.

Effect of Plasticizers:

Effect of plasticizer on tensile strength of the films was determined using texture analyser. Different concentrations of plasticizer films were evaluated for its tensile strength[24].

In-*vitro* drug release

USP – Type 1 (basket) apparatus, was used for *in vitro* release study from GIMAPS formulations. The dissolution medium used for the study was 0.1 N HCl for initial 2hrs followed by 500ml phosphate buffer pH 6.8 for 6hrs. The release was performed at 37°C±0.5°C, with a rotational speed of 50rpm. Samples (5ml) were withdrawn at predetermined time intervals and replaced with fresh medium .The samples were filtered through Whatman filter paper No. 41 and analyzed by UV spectrophotometer at 218nm.

QbR: Here the GIMAPS were taken in an enteric coated capsule shell and hence placed in the basket during the study.

In this study, the effect of various mucoadhesive polymers and its ratios on the release behavior and kinetics of DLX from GIMAPS were evaluated. In order to describe the kinetics of drug release from GIMAPS, various mathematical models have been used.The drugrelease data were fittedfor zero-order (r_0),first-order (r_1)andHiguchi-type (r_H) release kinetics.Release rates were calculated from the slope of per cent cumulative release *vs.* time (*t*), log per cent drug remaining *vs.* time (*t*) and per cent cumulative release *vs.* the square root of time ($t_{0.5}$), respectively. The co-efficient of cor-relation of each of these release kinetics was calculated and compared[25].

RESULT AND DISCUSSION

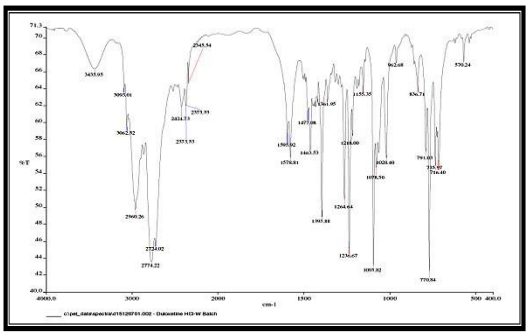

Figure 1: FTIR- ATR spectra of drug, Duloxetine HCl

The IR spectral analysis of DLX alone showed that the principal peaks were observed at wave number 2960cm-1 (C-H alkyl methyl bond), 2774cm-1, 1578cm-1 (C=C aromatic bond), 1463cm-1 (C-H alkyl methylene bond), 1395cm-1 (N-O aliphatic compound), 1236cm-1, 1095cm-1 (C-O alcohol secondary compound), 770cm-1 (C-X Chloro alkane compound). Figure4.28 represents the reference spectra 83of. This was found to be comparable with characteristic peaks observed at wave number 3435cm-1,3095cm-1,3062cm-1,2960cm-1,2424cm-1,2333cm-1,1595cm-1,1528cm-1, 1263cm-1, 1236cm1, 1098cm-1 etc. Hence structure elucidation test using IR Spectra also confirms that the test substance is DLX.

X-Ray Diffraction

From the XRD pattern of the drug shown fig 1, we can confirm that there were no polymorphic forms existing in the drug procured. However, the sample used for the study showed characteristic peaks mentioned in prior literature[83]. When compared with the standard XRD pattern from the, similar characteristic peaks were obtained as explained below

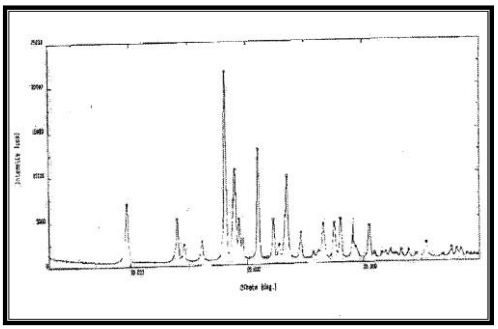

Figure 2: Reference X-Ray Diffraction pattern of drug

Drug quantification/Quantitative analysis Spectroscopy method (UV)

For the purpose of drug Quantification in solubility studies, standard curve was determined in pH 6.8 phosphate buffer solution and absorbance obtained

Optimization trials

Optimization trials for GIMAPS were performed as per table 2. Here Ethyl Cellulose and Eudragit RSPO were chosen in the trials with different mucoadhesive polymers. Mucoadhesive layer showed lot of air entrapment and gel-like formation. Decision was taken to add/mixmuco adhesive polymer during the preparation of the drug layer during the processing time.

Table 2: Final Formulation Table

Ingredien t (%)	FP 1	FP 2	FP 3	FP 4	FP 5	FP6	FP7	FP 8	FP 9	FP10	FP11	FP12	FP13	FP14	FP15
Drug DULOXE TINE HCL(mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Ethyl cellulose (10cps)	10	5	10	5	10	5	10	5	10	5	-	-	-	-	-
Eudragit RSPO	-	-	-	-	-	-	-	-	-	-	3	3	3	3	3
HPMC– 5cps	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Carbopol 971PNF	1.5	1.5	-	-	-	-	-	-	-	-	1. 5	-	-	-	-
Carbopol 974P	-	-	1.5	1.5	-	-	-	-	-	-	-	1.5	-	-	-
Sodium CMC	-	-	-	-	2	2	-	-	-	-	-	-	2	-	-
Polycarbo phil	-	-	-	-	-	-	2	2	-	-	-	-	-	2	-
HPC	-	-	-	-	-	-	-	-	2	2	-	-	-	-	2
Eudragit EL100	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

in UV spectrophotometer are mentioned in Table 2. Similarly, standard linearity curve was plotted for quantification of DLX from *in-vitro* samples.[26]

Standard plot in pH 6.8 phosphate buffer solution gave linearity (R^2) within the acceptable limit i.e. 0.9990 and 1.0000.Thus, the UV linearity plots were found acceptable and considered for assay of drug in samples for solubility and *in-vitro* studies respectively. shows the linearity plot for standard solutions of Duloxetine HCl.

Table 3: Standard solutions absorbance for DLX in pH 6.8 phosphate buffer

Concentration(ppm)	Absorbance
2	0.15780±0.009
4	0.29303±0.006
6	0.43280±0.011
8	0.57663±0.008
10	0.71310±0.006
12	0.85283±0.002
Equation of line	Y=0.0697*conc.+0.0164
R^2	0.9999

Final procedure and formula

Final formula (Table 4) remained the same, but the procedure was modified. Mucoadhesive polymer was added to the drug layer solution during the process. Final patches were packed in aluminum foil and stored in desiccators to maintain the integrity and elasticity of the patches. These formulations were further subjected to various evaluations [30]. After the tensile strength evaluation of the above said batch of FP1 – FP15, slight modification were done on the final compositions of batches, coded F6-F20. Here the mucoadhesive polymer and drug layer polymer are taken in proper proportion as described in table 3.

Table 4: Final composition of formulation for GIMAPS

Formulation code	Ratio of mucoadhesive and HPMC polymers in percentage					
	Carbopol 971PNF	Carbopol 974P	Polycarbophil	Sodium CMC	HPC	HPMC-5cps
F6	25	-	-	-	-	75
F7	50	-	-	-	-	50
F8	75	-	-	-	-	25
F9	-	25	-	-	-	75
F10	-	50	-	-	-	50
F11	-	75	-	-	-	25
F12	-	-	25	-	-	75
F13	-	-	50	-	-	50
F14	-	-	75	-	-	25
F15	-	-	-	25	-	75
F16	-	-	-	50	-	50
F17	-	-	-	75	-	25

Physical evaluations

GIMAPS from batch F6 to batch F20 were colorless; odorless; soft and flexible films with

homogeneous surface and easy peel able from their substrates.

Folding Endurance

The folding endurance values were found to increase with an optimum concentration of plasticizer[27]. The folding endurance values of matrix films were found to be within 150–200 indicating good strength and elasticity, which is explained by the linear nature of the cellulose structure. The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The results indicate that the patches will not break and will maintain their integrity during use.

Flatness

Flatness study results showed that none of the formulations had different strip lengths before and after longitudinal cut, signifying 100% flatness, and thus indicating maintenance of smooth surface when attached to the target site.

Moisture Content

All the GIMAPS formulations from batch F6 to batch F20 were evaluated for LOD and found to be in acceptable range of 2%-4%.

Thickness Uniformity

For thickness uniformity of GIMAPS, patches were measured by using vernier calipers. The measurements were performed on 10 different randomly selected patches from each batch and thickness measured at six different points in order to evaluate the statistical difference, if any[33]. The homogeneity of film formulations in thickness is evaluated by these measurements. After measurements at six different points of and only selected patches of the batch, the results were expressed in terms of mean ± standard deviations.

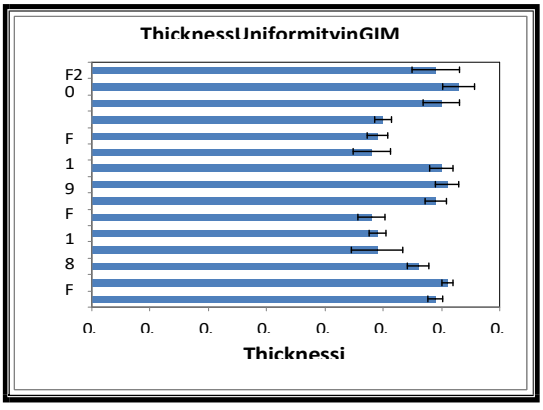

Figure 3: Comparison of thickness uniformity in GIMAPS in formulations batch F6 to batch F20

There was no significant difference found in thickness between the formulations, analysed by student's t-test ($p < 0.05$).

Weight Uniformity

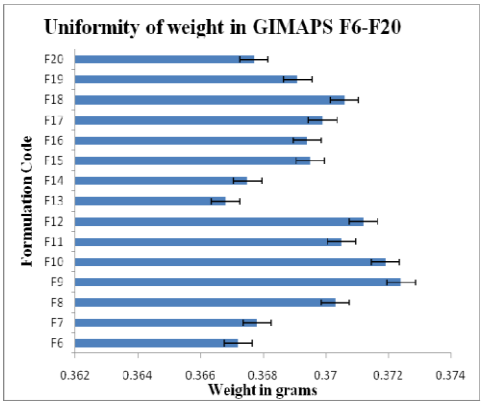

Figure 4: Comparison of uniformity of weight in GIMAPS in formulations batch F6 to batch

DRUGCONTENTUNIFORMITY

The patch of 4cm^2 area was dissolved in 50ml of phosphate buffer pH 6.8 and kept in orbital shakerfor24hrs at 50rpm at room temperature. After 24hrs of shaking, the solution was suitably diluted, and was measured for UV absorbance at 218nm against phosphate buffer pH 6.8 as blank. For each formulation three films were assayed individually. From each film batches, three GIMAPS were selected randomly and assayed by UV spectroscopy method[28].

Table 5:% Assay for optimized formulation

Formulation Code	Weight of the drug In GIMAPS (mg)	Absorbance*	Concentration In ppm	% Assay*
F6	20.36	0.2875±0.002	3.995	98.89
F7	20.11	0.2992±0.008	4.107	101.65
F8	20.23	0.2895±0.009	3.997	98.94
F9	20.14	0.2972±0.011	4.085	101.12
F10	20.25	0.2913±0.004	4.026	99.66
F11	19.97	0.2962±0.002	4.038	99.95
F12	20.16	0.2883±0.001	3.967	98.19
F13	20.12	0.2897±0.003	3.978	98.47
F14	20.27	0.2873±0.015	3.975	98.38
F15	20.30	0.2891±0.001	4.006	99.15
F16	20.31	0.2877±0.001	3.988	98.72
F17	20.18	0.2894±0.002	3.986	98.66
F18	20.34	0.2937±0.001	4.077	100.92
F19	20.15	0.2892±0.002	3.977	98.45
F20	20.31	0.2943±0.002	4.080	100.98

*Represents the values expressed as mean ± SD; n=3

Swelling Index

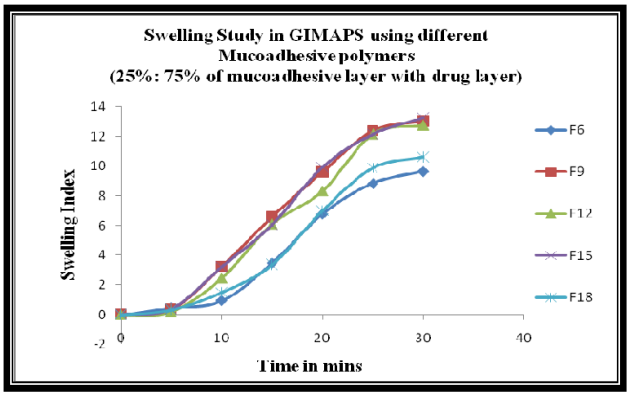

Figure 5: Swelling Index in GIMAPS batch of F6, F9, F12, F15 andF18 taken with 25:75 ratios of Mucoadhesive and HPMC polymer

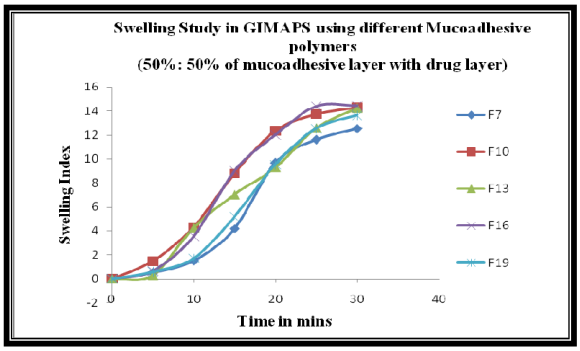

Figure 6: Swelling Index in GIMAPS batch of F7, F10, F13, F16 and F19 taken with 50:50 ratios of Mucoadhesive and HPMC polymer

Surface pH

Surface pH of all formulation batches of F6 to F20 of GIMAPS was found to range from pH 6.0 to pH 6.30 of acceptable limits. These results revealed that all formulations provided an acceptable pH in the range of intestinal pH (6.0 to 6.8) and that they would not produce any local irritation to the mucosal surface. This study also suggested that the polymeric blend identified was suitable for GI application owing to the acceptable pH measurements.

Water Vapour Transmission

From this evaluation the quantity of moisture transmitted through unit area of a patch in unit time was obtained. The water vapour transmission data through GIMAPS are important in knowing the permeation characteristics.

Table 6: Surface pH and water vapour trans mission in GIMAPS formulation batch F6 to batch F20 for 30minutes

Batch	Surface pH±S.D	Water Vapour transmission (gm.cm/cm^2.12hrs)
F6	6.22±0.02	5.23*10^{-4}
F7	6.11±0.13	6.55*10-4
F8	6.28±0.07	5.87*10-4
F9	6.21±0.15	5.83*10-4
F10	6.10±0.06	5.44*10-4
F11	6.02±0.07	6.14*10-4
F12	6.14±0.12	5.53*10-4
F13	6.02±0.11	5.34*10-4
F14	6.20±0.07	6.26*10-4
F15	6.13±0.15	4.98*10-4
F16	6.04±0.12	5.67*10-4
F17	6.16±0.13	5.26*10-4
F18	6.08±0.08	6.21*10-4
F19	6.21±0.04	5.98*10-4
F20	6.13±0.09	5.23*10-4

Tensile strength the valuation

Table 7: Tensile strength of GIMAPS in various plasticizer concentrations

S.No.	Sample ID	Max Load (N)	Load @ Break (N)	Tensile Strength @ max load (N/mm²)	Tensile Strength @Break load N/mm²	% age Elongation @max Load	% age Elongation @ Break
1	FTEC10	70.20	20.76	7.02	2.09	5.98	11.30
2	FTEC20	51.10	35.58	5.11	3.56	16.10	19.33
3	FTEC30	65.30	41.86	6.53	4.19	13.00	17.00
4	FPEG10	52.90	7.98	5.29	0.80	18.80	24.61
5	FPEG20	77.30	21.06	7.73	2.11	22.40	26.56
6	FPEG30	88.90	57.66	8.89	5.77	7.37	11.27
7	FPG10	25.10	8.49	2.51	0.85	17.60	29.82
8	FPG20	50.60	40.81	5.06	4.08	26.20	28.78
9	FPG30	73.00	72.56	7.30	7.26	13.20	14.17
10	FDBP20	66.00	47.92	6.60	4.79	7.13	11.11
11	F7	85.61	82.02	8.56	8.20	6.20	6.18
12	F10	76.41	72.14	7.64	7.21	5.90	4.90
13	F13	59.98	58.53	6.00	5.85	9.20	4.58
14	F16	46.31	43.21	4.63	4.32	12.10	10.42
15	F19	29.33	28.58	2.93	2.86	28.30	24.03

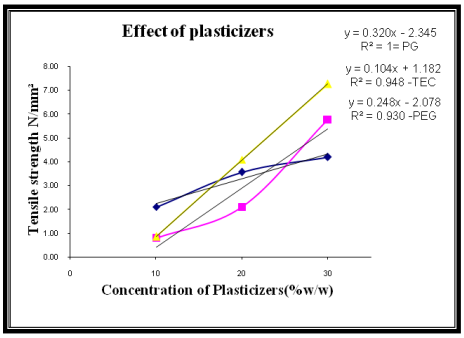

Figure 7: Effect of plasticizers on GIMAPS

In-*vitro* drug release

In swellable systems, factors affecting release kinetics are the liquid diffusion rate and the polymeric chain relaxation rate. When the liquid diffusion rate is slower than the relaxation rate of the polymeric chains, the diffusion is Fickian whereas when the relaxation process is very slow compared to diffusion, the case II transport occurs. When the liquid diffusion rate and the polymer relaxation rate are of the same order of magnitude, anomalous or non-Fickian diffusion is observed. On the basis of these considerations, it is clear that the drug released from GIMAPS is controlled by both drug diffusion and polymeric chain relaxation. Decrease in release rate values with the increase in polymeric grades and content increases the time needed to release a given quantity of drug, allowing higher hydration and relaxation of the polymer matrix, before release, which in turn shifts the release mechanism towards relaxation erosion. This may be due to the hydrophilic nature of the polymer used. The observed initial release may help to achieve the therapeutic plasma concentration of the drug in a short time along with a constant release rate for a longer period of time. Initial burst release was higher in matrix films formulated using a low viscosity grade polymers (HPMC 5cps) compared to higher viscosity grade polymers (HPMC 50cps). Hence the F6-F20 formulations were prepared by HPMC -50cps. Of the various formulations made using different concentrations of mucoadhesive polymers, formulations (F6-F20) were selected on the basis of the drug content and release pattern.

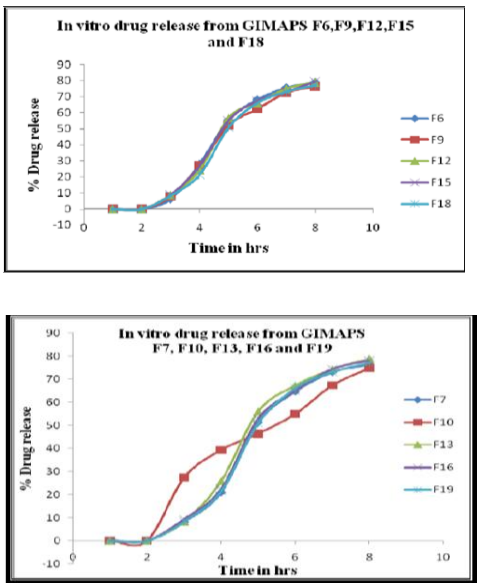

Figure 8: *In-vitro* drug release from GIMAPS F7, F10, F13, F16 and F19

Permeability study

A comparison on permeation study was performed by using different permeability membranes like dialysis membrane, egg membrane and porcine intestinal membrane.

Table 7: Comparison of permeability indifferent membranes

Time (min)	*DM	*EM	*Porcine Intestine
0	0.00±0.00	0.00±0.00	0.00±0.00
30	2.54±0.74	1.28±0.54	6.47±0.95
60	10.26±0.49	9.34±0.83	15.62±1.56
120	17.85±0.99	16.49±1.42	21.45±0.84
180	25.39±0.63	12.51±0.92	29.56±0.35
240	31.15±1.47	24.94±0.79	46.21±1.12
300	46.46±1.95	38.33±0.35	51.97±0.67
360	50.93	36.10±	60.12±0.76

*Average of mean ± S.D, n=3readings

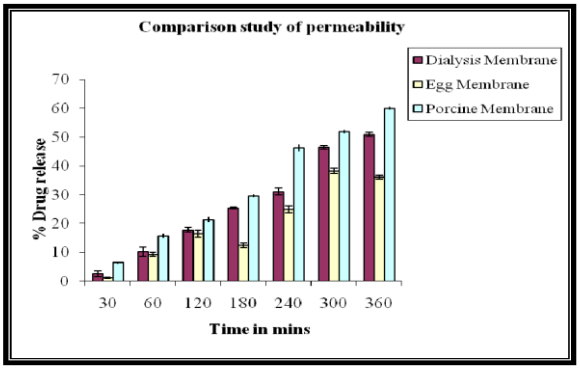

Figure 9: Comparison study of permeability

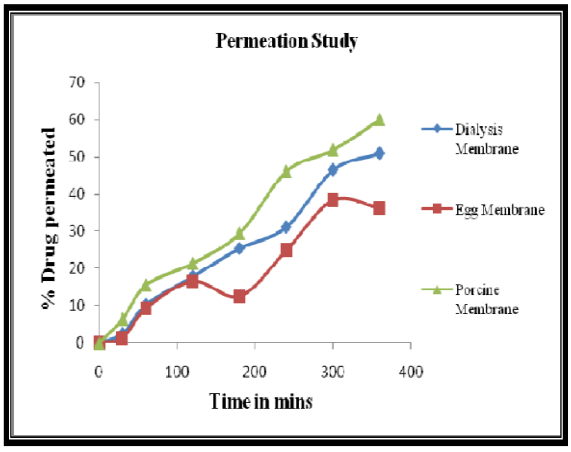

Figure 10: % drug permeated from different membranes

From this study it is understood that egg membrane gave erratic results whereas porcine membrane and dialysis showed better permeability with ~60% and 51% drug release respectively. During the study it was observed that the most challenging to achieve repeatability in results was the thickness of porcine intestinal membrane. Tissue preparation is also to be considered and most care should be taken for this study.

DISCUSSION

Pharmaceutical research is leading towards innovations in the area of drug delivery at much faster pace as compared to the last two decades. Vital aspects of a new drug delivery system are: improved patient compliance and effectiveness. Oral route offers an attractive and convenient route of drug administration, but its application is limited due to poor stability of peptides and proteins in the gastrointestinal tract. Transmucosal delivery is one of the modes that allow rapid uptake of drug into the systemic circulation avoiding first pass metabolism. This attributes to the relative permeability of mucous membrane. This type of delivery system allows drug to circumvent some of the body's natural defense mechanisms. Mucoadhesion refers binding of materials to mucin layer of a biological membrane. Mucoadhesive polymers are used in various dosage forms in order to achieve systemic delivery of drugs through the different mucosae. Mucoadhesive polymers should possess some salient physiochemical features such as predominantly anionic hydrophilicity with numerous hydrogen bond forming groups, suitable surface property for wetting mucus/ mucosal tissue surfaces and sufficient flexibility to penetrate the mucus network or tissue crevices. Mucoadhesion occurs in three stages like wetting, interpenetration and mechanical interlocking between mucin and polymer. Transmucosal drug delivery systems require balanced adhesive and cohesive properties of polymer. Mucoadhesion facilitates the intimate contact of the dosage form with mucosal layer, prolongs its residence time and enhances the bioavailability of the drug.

Gastro-Intestinal Muco-Adhesive Patch System (GIMAPS) is an approach for inducing greater levels of absorption and stability at the intestinal epithelium and administered as oral drug delivery system. This method involves the use of millimeter size mucoadhesive patches that adhere to the intestinal wall and direct solute diffusion towards the wall. It comprises layers of thin, flexible multi-membranes like an impermeable backing – water insoluble polymer; a drug reservoir; a rate controlling membrane and an adhesive. Gastrointestinal mucoadhesive patch systems (GIMAPS) have three key attributes like bioadhe sive properties for retention of the dosage form, controlled and unidirectional drug release towards the intestinal epithelium and drug protection. These intestinal patches provide protection from gastrointestinal degradative processes combined with site specific delivery to absorptive regions of the intestinal tract. This concept is purported to yield high local concentrations of the drug in close proximity with epithelial cell layer and hence transport across the barrier of the intestinal membrane.

The main objective of this research work was to design, develop and evaluate gastrointestinal mucoadhesive patch system (GIMAPS) of an anti – depressant for oral drug delivery. With the objective of using innovative approach to administer Duloxetine hydrochloride (DLX), formulations were designed as GIMAPS by ensuring drug protection in acidic environment and giving a controlled unidirectional release.

Drug of choice used in this research work was Duloxetine hydrochloride. It is a selective serotonin and nor-epinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+) - (S) – N – methyl – γ - (1-naphthyloxy) – 2 - thiophene propylamine hydrochloride. The approach in this research was to orally administer the patch which is stable in the gastric condition, and when the patch reaches the small intestine, the pH-sensitive layer dissolves and the muco adhesive layer makes it possible to attach on to the intestinal wall. Once the patch is attached, the drug is released simultaneously. On completion of the release and when the mucoadhesive property is lost, the patch detaches itself from the intestinal wall and is subsequently eliminates in faeces.

Preformulation studies were carried out to understand the physical and chemical characteristics and drug excipients compatibility. It was found that drug is soluble in organic solvents like methanol and acetonitrile and slightly soluble in water. Polymers like HPMC-5cps, Carbopol 971P NF and 974P are soluble in water, whereas Eudragit RSPO and L100 polymers are soluble in acetone. Duloxetinehydro chloride solution was found to have its maximum wavelength (λ_{max}) of absorbance in UV spectroscopy as 218 nm. Melting point of the drug was found to be1 66°C. IR spectra confirmed the results for identification tests of drug Duloxetine hydrochloride. Drug–excipients compatibility study was carried out by using IR, DSC and XRD. Results of this study indicated that the drug was compatible with excipients tested. SEM analysis was performed for the drug and excipients mainly to understand the morphological characterization of drug in the formulation (GIMAPS).The data generated was utilized for formulation strategy.

Analytical RP-HPLC method for Duloxetine hydrochloride was developed using potassium dihydrogen or tho phosphate buffer pH3.0 (include striethyl amine and pH3.0

In formulation batch F6-F20, a significant adhesion force (0.5–8.0 N/mm^2) was observed

between the patch and the mucosa over a period of 8hr, although there was no directed force to bring the patch in contact with the mucosa. An adhesion force of1N/mm^2 is quite significant and orders of magnitude greater than the detachment force arising from the weight of the patch. Long-term contact of the patches with the mucosa was confirmed by *ex-vivo* experiments, which demonstrated that about 90% o the patches adhered to the luminal wall by their Mucoadhesive side. No patches attached to the mucosa by their backing layer.

Films made with Carbopol971PNF, batch F7 showed highest Mucoadhesive time when compared with other films. Selected formulations were subjected to stability testing as per ICH guidelines. Three batches of each formulation were kept under different conditions of temperature and humidity for long term (25°C/60%RH), intermediate (30°C/65% RH) and accelerated conditions (40°C/75%RH). Samples were withdrawn at regular time intervals and percent assay was carried using HPLC method of analysis. Assay of the drug was determined and was found to be in the range of 98.0%-102.0%.

CONCLUSION

The present research work was aimed at design, development and evaluation of Gastro-Intestinal Muco-Adhesive Patch System (GIMAPS) for oral drug delivery. The present research has limited the problems associated with particles as drug carrier like transit of particles in GI tract generally causing high variability and acidic or enzymatic degradation and drug release.

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