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FORMULATION AND EVALUATION OF MUCOADHESIVE GASTRO-RETENTIVE TABLETS OF DOMPERIDONE

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ABSTRACT

Objective: This study was aimed at the formation and evaluation of the mucoadhesive gastro-retentive tablet of domperidone to overcome the drawbacks related to the oral administration of drugs. These gastro retentive formulations stay in the stomach for a longer time to provide prolonged gastric retention time. **Methods:** Mucoadhesive tablets were prepared by using Carbopol 940, sodium alginate, HPMC, and other polymer combinations in five formulations. Before tablet preparation, pre-formulation studies were performed i.e., bulk characterization, crystallinity, hygroscopicity, micrometric properties, melting point, particle size distribution, solubility, and stability analysis. The method of wet granulation was used for the formation of mucoadhesive gastro-retentive tablets of domperidone. Five formulations were evaluated for physical parameters using official methods mentioned in USP pharmacopeia, mucoadhesive strength & time, and swelling index. The USP-II dissolution apparatus with 1.2 HCl buffer was used for performing an in-vitro dissolution study for 24 hours. The optimized formulation was evaluated for compatibility studies using FTIR and DSC studies. **Results:** Among the five formulations the F5 was the optimized formulation because of its drug content, mucoadhesive strength, in-vitro drug release, and swelling index (7hr) of the optimized formulation 95.92 ± 0.62%, 26.98 ± 1.0gm, 93.16%, and 3.673% respectively. The release kinetics indicated that the F3 to F5 followed Higuchi's equation and non-fickian release which means F5 was dependent on both diffusion and dissolution thus the system is both diffusion and dissolution controlled. The resultant peaks of FTIR and DSC studies showed almost no drug-polymer interaction, which indicated physiochemical compatibility of drug and polymer in the optimized formulation. **Conclusion:** Hence concluded that the F5 was an optimized formulation that contained 84gm of Carbopol 940 and was found suitable for all performed evaluating parameters.

Keywords: Domperidone, Antiemetic, Mucoadhesive gastro-retentive tablet, Carbopol.

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INTRODUCTION

Domperidone is peripherally potent and Dopamine (D2) receptor antagonist is included in class 2 of the Biopharmaceutical Classification System (BCS) **[1]**, so it exhibits poor solubility with high permeability **[2]**. Domperidone has a high molecular weight **[3]**, being a weak base having high absorption in the acidic pH of the stomach and low absorption in the small intestine (alkaline pH) and neutral pH **[4,]**, having a first-pass effect, and having high hepatic metabolism by CYP3A4 leads to its low absolute bioavailability and subsequently leading to a therapeutic failure **[5]**. The half-life of domperidone is 7.5 hours and hence its dosing frequency is three times a day **[4]**.

Domperidone is used as an antiemetic and prokinetic so used to treat nausea and vomiting by antagonizing receptors of dopamine D2 in the chemoreceptor trigger zone **[6]**. The major off-label use of domperidone is to manage low breastmilk supply after birth in women **[7]**. In Australia, domperidone is indicated as a first-line galactagogue **[8]** but there's a gap in clinical evidence for dose, duration of treatment, targeted population, and long-term effect of its uses **[7]**.

Besides its uses, the most common adverse effect associated with domperidone is QT prolongation due to a delay in potassium current. At high doses, domperidone may cause cardiac death **[9, 10]**. This is

most common in elderly patients due to polypharmac. To minimize the cardiac risk-factor the Ministry limits the use of domperidone. Some other adverse effects of domperidone include dry mouth, cramps in the legs and stomach, sleeping discomfort, and irritability **[11]**. The mucoadhesive drug delivery system is proved to be beneficial for many routes of drug delivery such as nasal, stomach, buccal, rectal, and vaginal mucosa **[12]**. This system has the benefit that it can stick to mucus, a layer of mucus membrane **[13]**. This is based on incorporating adhesive materials in the pharmaceutical formulation during development **[14]** to enhance its residence time **[12]** which is the major issue for drugs absorption in GIT and contact with the absorption site for longer, releasing the drug and providing local effect **[14]** and increasing bioavailability **[15]**.

The control release parameter of the drug can also be better modified by changing the concentration of the polymer **[16]**. Polymers were examined to peer if they meet all the parameters (big quantity of hydrogen bonds, swelling qualities, good enough wetting, and chain flexibility of polymer) for mucoadhesive polymer diffusion to the mucous membrane community earlier than being utilized in any mucoadhesive method **[17]**.

Despite various advantages, the Mucoadhesive drug delivery system also has some disadvantages. These disadvantages further depend on the route of administration, polymers, and adhesion property of formulation **[18]**. But the major disadvantage of this system is the lack of a suitable model for the evaluation and in-vitro testing for the establishment of in-vitro in-vivo correlation **[18, 19]**. Due to this reason, bioequivalence studies have some limitations. Other than this, some drawbacks are also associated with the type of manufacturing process **[14, 19]**. Sometimes the adhesive property of this delivery system results in mucosal membrane injury when the formulation sticks more firmly **[18]**. But this problem is managed by maintaining the quantity and compatibility of respective polymers and additives **[14]**.

The main purpose of this study was the formation and evaluation of the mucoadhesive gastro-retentive tablet of domperidone to overcome the drawbacks related to the oral administration of drugs. These gastro retentive formulations stay in the stomach for a longer time to provide prolonged gastric retention and thus improved bioavailability when the drug was released in an exceedingly extended manner.

MATERIAL AND METHOD

Chemicals

Domperidone was a kind gift from SAMI Pharmaceuticals Pvt. Ltd. Pakistan, HPMC, Carbopol 934, Carbopol 940, Xanthan Gum, Guar Gum, Sodium Alginate, Starch, PVP K30, Mannitol, Chitosan, MCC (microcrystalline cellulose), Mg Stearate/Talc were purchased from Sigma Aldrich Pakistan and distilled water.

Pre-formulation Tests

Crystallinity

The degree of structural organization in a solid is known as crystallinity. A small quantity of domperidone was taken onto the glass slide. Two drops of water were put on the drug which was covered with the slip onto it. The glass slide was placed onto the stage of a microscope. Crystals were observed by using a microscope under different objective lenses.

Flow Properties

The Compressibility index also known as Carr's index and the angle of repose were used to find the flow properties of the drug by following formulas:

$$\text{angle of repose } = \tan^{-1}\frac{2\text{xheight}}{\text{diameter}}$$

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{tapped density}}\text{X}100$$

Size Distribution Analysis

The study of particle size distribution is termed micromeritics. For this purpose, we used the sieve method and find the % retained by using the formula:

$$\%\text{ retained } = \frac{\text{retained sample on the sieve}}{total\ weight\ of\ sample}X100$$

Hygroscopicity

Hygroscopicity is the tendency of solid/powder to absorb moisture from the surrounding environment. The Gravimetric analysis was used for moisture content determination during pre-formulation studies as

$$\text{Moisture Content } = \frac{\text{final wt}-\text{initial wt}}{\text{final weight}}\text{X}100$$

Melting Point Analysis

A melting point is a colligative property specific to a compound. Melting temperature is a characteristic figure and is used to determine the purity of a substance. The melting point of the sample was determined by utilizing the Fisher-Johns melting point apparatus.

Solubility Analysis

Standard buffer solutions of various ranges of pH between 1.2 and 8.0 were prepared according to USP and the solubility of domperidone in these aqueous buffers was determined. For knowing the solubility of domperidone in an organic solvent the Partition Coefficient was calculated by using the following formula:

$$\log \text{p} = loaqueousg\frac{\text{solubility in organic solvent}}{\text{solubility in aqeous solvent}}$$

Method of Tablet Preparation

Mucoadhesive tablets were prepared by using wet granulation method. The composition of all formulations was shown in table 1. All ingredients of formulation were weighed accurately and mixed thoroughly. Later, granulation was done using 5%

starch slurry as the granulating liquid. The dough was passed from the sieve no 20 and granules were dried at 40°C for 4 hours in the oven. Then again passed through sieve no 40. Dried granules were mixed with Mg Stearate using a tumbler and compressed by the force of a single punch tablet machine.

Swelling Index

Each formulation was individually weighted W1 and placed in Petri dishes that containing 4 mL acidic buffer of pH 1.2. Then removed the tablets from the petri dish at 1, 2, 3, 4, 5, 6, and 7 h. The excess water from surface of tablet was removed with filter paper carefully. Reweight the swollen tablets individually W2 and the (SI) swelling index was calculated using the formula:

$$\text{Swelling Index} = \frac{(W2 - W1)}{W1} X100$$

Mucoadhesion Time

10 tablets were randomly selected from each formulation for determining mucoadhesion time. The tablet was placed on rat stomach mucosa that freshly cut. This fresh mucosa was tied with tape (double-sided) on the glass slide then 1 drop of HCl buffer was used to wet the tablet and the table was pasted on the mucosa by light force applying with a fingertip only for 30 seconds. At the bottom of the USP Type-II dissolution apparatus (DS 8000) placed the glass slide. The HCl buffer (900 ml) was used in this test at 37 ± 1°C. After 2 min, to simulate the stomach environment the stirring rate of 50 rpm was applied for 24 h and adhesion of tablet was monitored. The time at which the tablet detached from mucosa was noted that was the mucoadhesion time of tablet.

FTIR Analysis

The drug and excipients compatibility was checked using FT-IR spectra that is recorded with FT-IR 8400S Shimadzu spectrophotometer for 30 times through the wavelength of 4000-400 cm^{-1}. The compatibility of pure drug and polymer was analyzed by the comparison of all the spectrum obtained.

DSC Analysis

The compatibility study of a drug was carried out using (DSC) Differential Scanning Calorimetry.

By using a (DSC 4000; PerkinElmer, Waltham, MA, USA) the DSC studies conducted on domperidone DOM, Carbopol CP, sodium alginate SA, and the physical mixture of mucoadhesive tablets. The results obtained demonstrate the crystal pattern of the pure drug and interactions between other ingredients of the tablet. For this purpose sample (5mg) was weighed on the aluminum pan and the sample was heated with a heating rate of 20°C per minute from 100°C to 280°C under N_2 flow at the rate of 30 mL/min. By comparing peaks of the resultant thermogram, compatibility was analyzed **[20]**.

Content Uniformity

5 tablets of every formulation were crushed, and the 10th part by weight of each tablet was taken. The crushed contents of 10 tablets were dissolved separately in 10 ml HCl Buffer, stirred for half hour, and stored at room temperature for 24 hours. The next day, the sample was centrifuged at 4000 rpm (revolution per minute) for 15-30 minutes and 1ml of separated supernatant was diluted with 9ml buffer before running it at a wavelength of 286 nm on a UV spectrophotometer.

$$\text{Drug Content} = \frac{\text{Actual Yield}}{\text{Theoretical Yield}} X100$$

Table 1: Composition of mucoadhesive domperidone formulations.

Ingredients	Concentration (mg)				
	F1	F2	F3	F4	F5
Domperidone	10	10	10	10	10
HPMC K4M	-	-	84.7	50	
Carbopol 934P	-	-	80	-	
Carbopol 940	36	-	-	-	84
Xanthan Gum	-	30	-	30	
Quar Gum	-	30	-	-	
Sodium Alginate	-	-	-	40	70.8
Starch	-	-	-	50.0	
PVP K30	12	-	-	-	
Mannitol	18	-	-	-	
Chitosan	-	40	-	-	
MCC	100	30			
Mg Stearate	3	5	5	0.2	1.22
Talc		5	-	-	
Total Weight	180	180	180	180	180

Standard Calibration Curve

A standard curve is use for determined a concentration of a specific substance from any unknown sample by comparing the curve of unknown substance from a set of standard samples whose concentration is known. 5mg of the drug was taken and diluted with 20ml buffer and a stock solution (200µg/ml) was made from this stoke solution 1ml was taken and diluted in 9ml buffer to form a working solution (20µg/ml) then 6 dilutions from the working solution of 2µg, 4µg, 6µg, 8µg, 10µg, and 12µg/ml were formed.

Dissolution Analysis

The release of drug in vitro was measured through USP dissolution apparatus II. The dissolution medium was comprised of 900 mL HCl buffer of pH 1.2 set at 37°C ± 0.5°C. One tablet from each formulation was placed in 5 flasks and apparatus was set at 50 rpm. Sample was taken at 0,0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours. 1 ml sample was taken every time and added into a test tube containing 9 ml of buffer separately. Then this 10 times diluted samples were analyzed on the spectrophotometer at a wavelength of 286nm. From this the percentage release curve was calculated. This curve provided the information about the amount drug that would be released from the delivery system.

RESULT AND DISCUSSION

Pre-formulation Tests

The pre-compression tests and their results of domperidone were listed in **Table 2**.

The solubility of domperidone was analyzed in the various aqueous buffers of pH 1.2 – 8.0 and organic solvents. Results of the analysis show that domperidone was very slightly soluble at acidic pH and very soluble in organic solvents as shown in Table no 3. Similarly, the Partition Coefficient (log P) value of domperidone was 2.9 which made it a hydrophobic drug **[21]**.

Post-formulation Tests

This research work showed the preparation and evaluation of domperidone gastroretentive mucoadhesive tablets. Wet granulation method was used for the formation of Domperidone tablets were prepared that continuously release drug content for 12 h in the upper GIT i.e., the stomach. Physical characteristics were evaluated by various tests i.e., appearance, thickness, weight variation, friability, and hardness. All batches of five formulations passed these tests as shown in **Table 4**. Various post compression parameters were determined for each formulation

Table 2: Outcomes of various pre-compression parameters.

Method Name	**Result outcomes**
Crystallinity	Bound and Crystalline.
Flow Properties	The angle of Repose= 260-290°; Compressibility Index= 9.33-15.86%
Particle Size Distribution	Size range: Bw18 and 24 mesh
Hygroscopicity	MC is 2.6%.
Melting Point Analysis	Started at 236°C; Completely at 241°C.

Table 3: Solubility of 1 part of Drug in 1 part of Solvents.

Buffer Solution/ organic solution	**Parts of Buffer to dissolve I part of drugs**	**Inference**
HCl Buffer pH 1.2	1730 Parts	Very Slightly Soluble
Phosphate buffer pH 5.8	4813 Parts	Very Slightly Soluble
Dimethyl Sulfoxide	0.07 Parts	Very soluble
Acetone	0.99 Parts	Very soluble

Table 4: Outcomes of various post compression parameters.

Formulation (N=10)*	**Hardness**	**Friability**	**Thickness**	**WV[1]**	**MAT[2]**	**MAS[3]**	**SI[4]**	**DC[5]**
	Kg/cm^2±S.D	%	mm ± S.D	mg ±S.D	hour ± S.D	gm ± S.D	%	% ± S.D
F1	4.64 ± 0.4	0.44	4.49± 0.03	664.4±2.5	10.00±0.6	26.81 ± 0.8	3.402	94.57± 1.33
F2	4.87±0.6	0.48	3.01±0.03	664.9±1.9	10.98±1.0	26.91 ± 1.0	3.419	96.64 ± 1.43
F3	4.90 ± 0.6	0.49	4.51 ± 0.03	658.2±2.0	10.66±0.8	27.06 ± 1.1	3.568	67.02 ± 1.41
F4	4.81 ± 0.6	0.42	4.512 ± 0.04	661.3±2.1	11.56±0.6	26.54 ± 1.2	2.672	98.43 ± 1.63
F5	4.79 ± 0.3	0.39	4.52 ± 0.02	661.8±2.0	12.01±0.5	26.98 ± 1.0	3.673	95.92 ± 0.62

[1]Weight Variation, [2]Mucoadhesive time, [3]Mucoadhesive strength, [4]Swelling Index, [5]Drug Content

The normal range of hardness for tablets according to USP is 4-8 kg/cm^2. The hardness of our tablets was found to be in the range of 4.64±0.4 to 4.90±0.6 and hence test was passed by them.

The thickness of a tablet should facilitate the swallowing of the tablet by the patient with an acceptable thickness. All the tablets should fall within a standard range of ±5% for uniformity. Our tablets were cylindrical and had an acceptable thickness thereby not affecting patient compliance.

The weight variation test is a non-destructive test that compares the individual weights of tablets with their average weight. According to the mentioned standard, tablets fell in this range and hence test was passed by them. The limit of friability for all tablet dosage forms according to BP is <1%. Our tablets had a friability below the acceptable limit and hence test was passed by them.

Swelling Index

The swelling index has Significant importance in adhesion because the adhesion of tablet to mucosa occurs after tablet starts to swell. From the results mentioned in table no 4 it could be seen that the F5 formulation, prepared with Sodium alginate and Carbopol showed maximum swelling index.

Mucoadhesion Strength and Time

The mucoadhesive properties of a delivery system is effected by the nature and amount of mucoadhesive polymer used. All the formulation showed maximum mucoadhesive strength i.e., the best values of MAS in gram were shown by F3 followed by F5, F2, and F1. While F4 showed the minimum strength.

The gastric residence time of the any formulation is determined by the time of adhesion i.e., the mucoadhesion time of the tablet. The longest time of adhesion was shown by F5 followed by F4. Meanwhile, F1 showed the shortest duration of adhesion.

Content Uniformity

The drug content was showed in the range of 92.7 to 98.9% for all formulations which reflects good uniformity among formulations as per standard. But F4 showed a 98% release of drug which was the highest among all.

FTIR Analysis

The formulation mixture containing domperidone, Carbopol and sodium alginate had given the similar spectrum to the spectrum of pure drug. The characteristic bands observed in pure domperidone, and physical mixture were: -NH stretching vibration (3300-3500 cm^{-1}), - C-H stretching vibration (2800-3200 cm^{-1}), -CO-R-vibration (1710 cm^{-1}), and C-N stretching vibrations (1250-1020 cm^{-1}). Analysis of principal peaks indicated no major changes or chemical interaction and proved the drug and polymers to be compatible **[22]**. Peaks of drug and other excipients were separated apart as shown in **Fig. 1**.

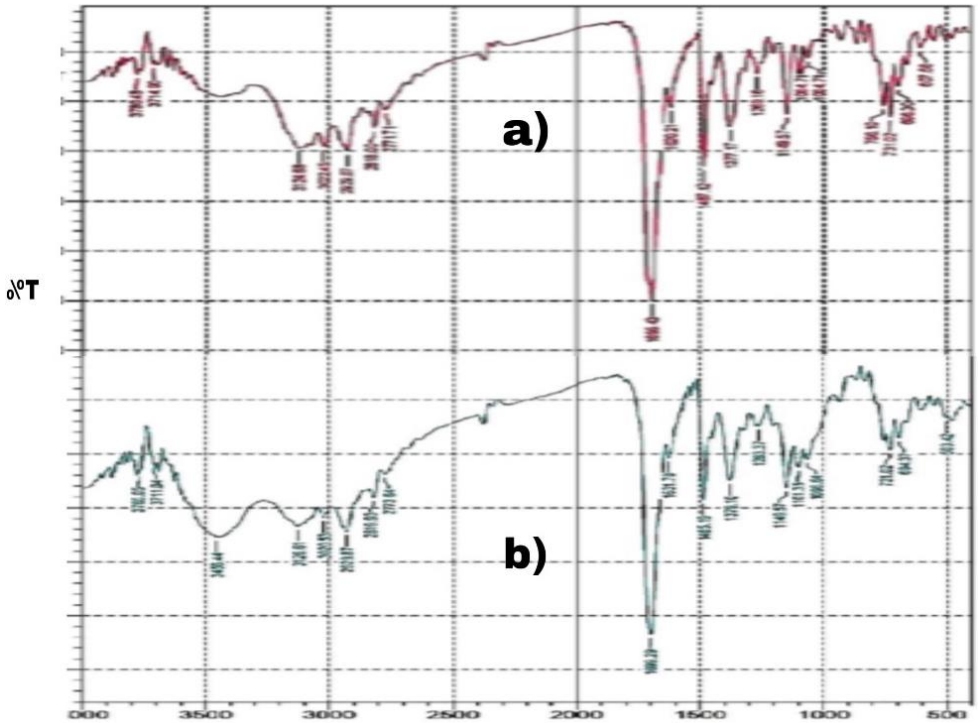

Figure 1: FTIR spectra of drug and physical mixture. (a) The pure drug, (b) The drug and polymers.

DSC Analysis

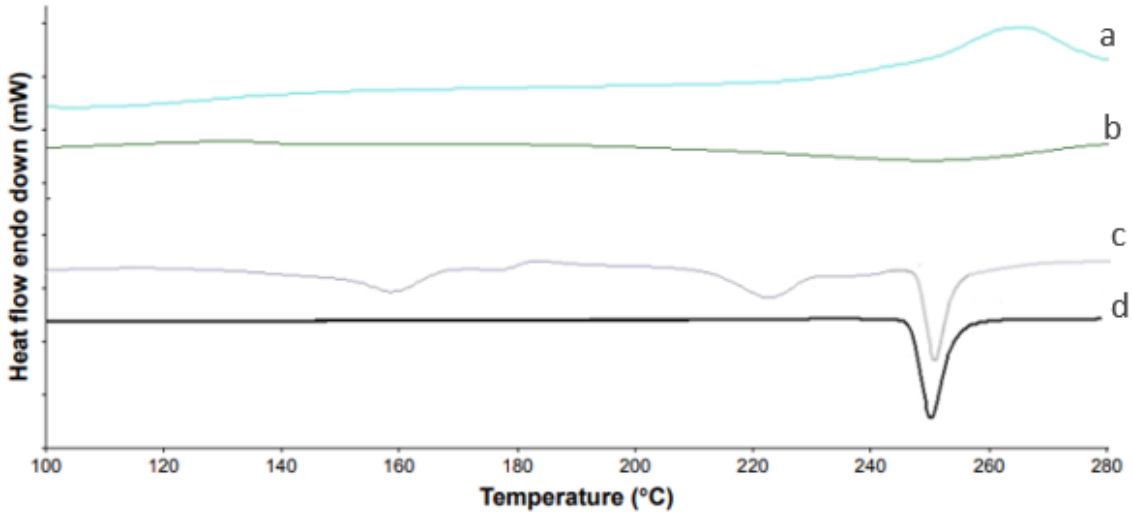

Figure 2: DSC thermogram of drug, polymers, and physical mixture. a) Sodium alginate SA (b) Carbopol 940 cP (c) Physical mixture (d) Domperidone

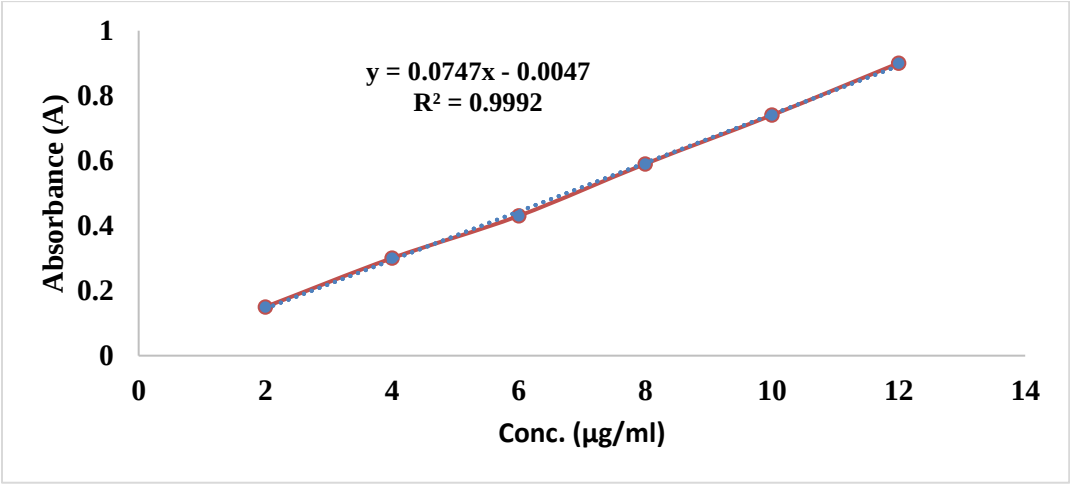

Figure 3: Standard calibration curve of domperidone.

The Chemical incompatibilities included degradation hydrolysis or oxidation and the incompatibilities of solid-state included the solubilization or polymorphism could be determined by variation in peaks of DSC thermograms of physical mixture by using domperidone (pure) as a reference standard. The domperidone showed a endothermic peak that started melting at 247.15°C and a sharp peak at 249.15°C with a enthalpy of 112.13 J/g. The resultant DSC thermograms of DOM, SA, CP, and mucoadhesive tablet (physical mixture) showed no prominent changes in the melting temperatures, shape of the peaks, and thermal profiles of tablet ingredients (polymer and excipients) in the formulation as shown in **Fig. 2**. By this, it was proved that there were no major shifts and indicated that no physical and chemical interactions

Standard Calibration Curve

The calibration curve of standard solution dilutions was performed to compare the unknown analyte concentration using straight line equation. The maximum correlation was evident of accurate response calculation (**Fig. 3**).

Dissolution Analysis

Dissolution analysis was done to check the release of the drug at different time intervals. The pores formed in tablets were observed after the dissolution was performed. The absorbance values of our optimized formulation F5 at different time intervals for 24 hours dissolution studies were 0.005, 0.013, 0.018, 0.024, 0.029, 0.037, 0.043, 0.049, 0.056, 0.063, 0.071, 0.0775 at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours respectively (**Fig. 5**).

Tablet before dissolution and after dissolution are shown in **Fig. 4**.
The initial weight of tablet before adding to dissolution medium was 180mg.

The final weight of tablet after 24-hour dissolution was evaluated 383mg that was evident of swelling of tablet and porosity that allowed the drug to diffuse from tablet into the medium at a sustained rate.

(a) (b)

Figure 4: (a) Tablet before dissolution (b) Tablet after dissolution.

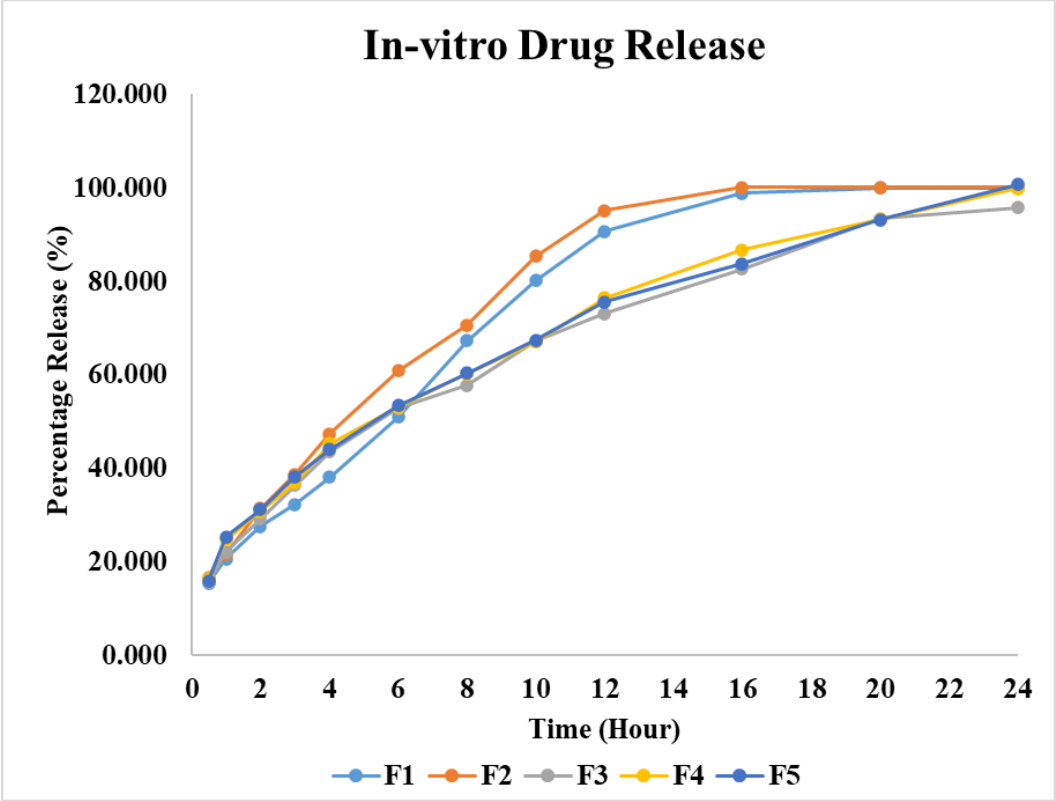

Figure 5: *In-vitro* drug release of mucoadhesive gastro-retentive tablets of domperidone.

Kinetic Modeling of Drug Release

DDSolver program was used to model the *in-vitro* release of the drug and determine which model is followed by the formulation. This also aided in the determination of the optimum formulation from all the formulations. Various models are followed by sustained-controlled release systems which include: Zero Order Model, Higuchi Model, First Order Model, and Hixson Crowell Model. Whether a formulation follows a model is determined by 3 parameters: R-squared value, Akaike Information Coefficient (AIC) & Model Selection Criteria (MSC). For a formulation to follow a model, it should fulfill at least 2 of the 3 conditions: a) R2 value should be ≥ 0.95 b) AIC should be < 50 c) MSC should be > 3. If a formulation fulfills at least 2 conditions, it follows the model, and this is confirmed by the Korsmeyer-Peppas Equation.

AIC estimates the quality of each model, relative to each of the other models. Based on observed data the Model selection criteria are used to select a statistical model among a set of candidate models. To be able to follow the zero order or first order of reaction AIC and MSC values should be 0.97 to 0.99, 30, and 3-4 respectively, which is unlikely in our case so none of the formulations follow zero order reaction or first-order reaction.

The Higuchi model gives the drug release as a function of the square of the time. According to the table no. 3.2, formulations F3, F4, and F5 followed the Higuchi model because their R2 values, AIC, and MSC fall under the selection criterion. This showed that the formulation prepared is a diffusion-controlled release. The value of R2 adjusted, AIC, and MSC of formulation F3 were 0.9937, 48.9019, and 4.8990 respectively. While the value of r2 adjusted, AIC and MSC of formulation F4 were 0.9934, 49.9689, and 4.8468 respectively and the value of R2 adjusted, AIC and MSC of formulation F5 were 0.9945, 47.4840, and 5.0347 respectively and its release time data was 0.891, 3.563 and 9.120 at T25, T50 and T80 respectively. Our best/ ideally fit formulation was F5 which had R^2 adjusted value of 0.9945, AIC value of 47.4840, and MSC value of 5.0347, and its release time data was 1.434, 5.735, 12.904, 14.682, and 18.582 at T25, T50, T75, T80 and T90 respectively. So, our delivery system was concentration independent and dependent on any factor of time and had a positive K value. Diffusion release was seen in our system.

It can be seen from the table that the formulations F3, F4, and F5 passed this confirmatory test according to their R square adjusted values, AIC, MSC, and N values. N values of formulation F3, F4, and F5 were 0.469, 0.465, and 0.462 which lay between 0.45 to 0.89. So, they all were regarded as an anomalous release or non-Fickian release. The system was found to be deviating from Fick's law of diffusion. It was a hydrogel and followed combined dissolution and diffusion-controlled systems. It was somehow following Fick's law also. But of all the formulations F5 formulation was the most suitable one with the N value of 0.462.

CONCLUSION

Out of the five formulations the F5 composed of sodium alginate and Carbopol 940 was found to be the optimized formulations due to its drug release that was 93.16% and its consistent release rate for 20h. Graphical studies of the F5 formulation to Higuchi's equation has shown the system is both diffusion and dissolution controlled. Hence the F5 formulation achieved the aims of this research that were to reducing the side effect mainly related to the higher dosing frequency, prolonged the half-life in drug plasma, avoiding first-pass metabolism, and improved patient compliance. From all findings it was concluded Domperidone as gastroretentive mucoadhesive tablets would be administered orally. As follow up of this work the in-vivo studies on animals, the pharmacokinetic studies, and controlled clinical studies on a human can be carried out in the future research.

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