Development of Fast Dissolving Buccal Patches of Prochlorperazine Maleate for Effective Management of Emesis

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ABSTRACT
The goal of this research was to increase the oral bioavailability and avoid the first pass metabolism of Prochlorperazine Maleate (used to treat nausea and vomiting) by creating its buccal patches. Prochlorperazine is a member of BCS II and has an oral bioavailability of 11–15%. Prochlorperazine maleate buccal patches were made by solvent casting with the aid of HPMC E-15 and Chitosan (film-forming agents), Glycerol (plasticizer), Tween 80 (penetration enhancer), Citric Acid (saliva stimulating agent), Mannitol (sweetening agent), and Ethyl Cellulose (Backing membrane). Twelve total formulations was made by using different quantities of polymers and formulation was evaluated for weight variation, thickness, folding endurance, drug content, in- vitro diffusion, in vitro, bio-adhesion time, percent moisture loss, % swelling index and stability study. Based on results it was concluded that buccal patches (F4) showed enhanced bioavailability.

Keywords*: Prochlorperazine maleate, Buccal Patches, Bioavailability, Stability*

1. Introduction

The oral cavity is a distinct place for drug delivery due to ease of administration, prevention of probable drug degradation in the GIT, and first pass metabolism [1]. Due to the highest level of patient acceptance, oral routes are most frequently used by manufacturers and medical professionals. Oral solid dose forms are available for around 60% of all dosage forms [2]. The company switched to parenteral and liquid orals because of the delayed onset times, decreased bioavailability, and low absorption rates. However, the main issue with liquid orals is proper dosage, and parenteral drug administration is uncomfortable, which causes the majority of patient noncompliance [3]. Medications should not be administered orally since doing so results in liver and gastrointestinal tract enzymatic breakdown, which prevents the absorption of many types of drugs, including peptides and proteins. The buccal region appears to be one of the favoured locations inside the mouth mucosal cavity for systemic medication distribution. It advantages include enhanced enzyme flora for medication absorption and the avoidance of hepatic first pass metabolism within the gastrointestinal system**[**4].

The lamina propria and submucosa are stratified, or separated, from the squamous epithelium lining the buccal cavity. The buccal mucosa is 4–4,000 times more permeable than the epidermis and less permeable than the intestine. Therefore, the buccal administration provides an excellent platform for molecules with low skin penetration to be absorbed[5].

Among the phenothiazine antipsychotic medications utilised is prochlorperazine maleate. It is utilised in the management of nausea, drug-induced emesis, and vomiting brought on by migraines (or other severe headaches). Its tablet dosage form has an oral bioavailability of around 12- 15%. In order to avoid the first pass metabolism and boost patient compliance, we might increase the oral bioavailability by forming it into buccal patches.

In the present study, an effort to improve Prochlorperazine maleate's limited bioavailability due to substantial hepatic or GI metabolism, mucoadhesive buccal patches have been developed and evaluated. Chitosan was used as a film-forming polymer together with HPMC E-15 to create a total of twelve formulations.

2. MATERIALS AND METHODS

2.1 Materials

Prochlorperazine maleate, HPMC E-15 & Ethyl cellulose was obtained from Yarrow chem. pvt. Ltd, Mumbai. Chitosan, Propylene glycol, Mannitol, Tween 80, Citric acid was obtained from Loba chemicals.

2.2 Methods

2.2.1 Physical appearance:

The several organoleptic qualities of prochlorperazine maleate, such as colour, odour, texture, and taste, were used to evaluate by its outward appearance [6].

2.2.2 Melting point determination:

The capillary fusion method was used to measure the melting point of prochlorperazine maleate. A little amount of medication was placed inside a capillary that was sealed at one end, and the capillary was then positioned with the sealed end facing down into the melting point

device. Using the given thermometer, the temperature at which the solid medication becomes liquid was recorded. The melting point was recorded and compared with literature value [6].

2.2.3 Fourier transform infra-red spectral analysis:

For the purpose of qualitative chemical identification, FTIR analysis of the material was performed. The infrared spectrum of Prochlorperazine Maleate was performed on the Fourier Transformed Infra-red Spectrophotometer. The sample was scanned at wavelength 4000-400 cm^{-1} [6].

2.2.4 Determination of solubility[7]:

2.2.4.1 Qualitative Solubility of Prochlorperazine Maleate in Different Solvents:

The solubility of Prochlorperazine Maleate was determined in different solvent systems. In screw-capped glass tubes, a little quantity of the drug was combined with 10 ml of each solvent and shaken on a continual water bath shaker for 24 hours at 25°C. Physical testing was done on the solutions to determine whether or not there were any drug particles.

2.2.4.2 Quantitative Solubility Prochlorperazine Maleate:

10 mg of the drug was dissolved in 10 ml of distilled water and 10 ml of phosphate buffer pH 6.8 in 10 ml volumetric flasks to assess the solubility of prochlorperazine maleate in these solutions. The mouth of flask was properly covered with aluminium foil and placed in water bath shaker maintained at 37°C for 48 hrs, Samples were taken manually and filtered.Using a UV spectrophotometer (Shimadzu-1900 UV-Visible spectrophotometer), solutions' UV absorbance was measured at 255 nm, and the quantity of medication dissolved was estimated using a calibration curve.

2.2.5 Partition coefficient:

The lipophilicity and cell membrane-crossing potential of a drug are measured by the partition coefficient. In n-octanol: phosphate buffer pH 6.8, the partition coefficient of prochlorperazine maleate was calculated. In a separating funnel, 10 mg of the drug was precisely weighed and added to 50 ml of n-octanol:phosphate buffer (1:1). Continuous shaking was applied to the mixture until equilibrium was reached. Distilled water was filtered using Whatman filter no. 41 after phases were separated using a separating funnel. Utilizing a UV spectrophotometer, the absorbance at 255 nm was measured to estimate how much prochlorperazine maleate was solubilized in phosphate buffer. Calculating the partition coefficient and comparing it to literature values[6].

$$P_{o/w} = C_{organic} / C_{aqueous} \ldots\ldots\ldots(1)$$

2.2.6 Determination of absorption maxima (λ_{max}) of drug:

By scanning a 10 µg/ml solution of the drug in methanol, phosphate buffer (pH 6.8), and distilled water between 200 and 400 nm, the UV absorption maxima of the drug were identified. The absorption maxima of pure drug in Methanol, Distilled water & Phosphate buffer pH 6.8 was observed [6].

2.2.7 Preparation of calibration curve of prochlorperazine maleate:[6]

Using a Shimadzu 1900I UV visible spectrophotometer, the calibration curves for prochlorperazine maleate were created in methanol, distilled water, and phosphate buffer pH 6.8. A 50 ml volumetric flask containing 50 mg of Prochlorperazine Maleate was accurately weighed, and the remaining volume was filled with distilled water and co-solvent to create a 1000 µg/ml stock solution of Prochlorperazine Maleate. From the stock solution, 1 ml was collected, placed into a 10 ml volumetric flask, and the remaining volume was filled with

solvent to create a solution with a concentration of 100 µg/ml, from which further dilutions of 5, 10, 15, 20, and 25 g/ml were created. To construct a calibration curve, the same process was used for methanol and phosphate buffer pH 6.8.

2.2.8 Drug – polymer interaction studies:

Before formulating the buccal patch, it is necessary to check the interaction between the drug and polymer used in the formulations. The physical mixture of drug and excipient were filled in vial an kept for interaction studies for 4 weeks and the vial were examine at regular interval for discoloration, Liquefaction, and clump formation in the mixture. Interaction between the drug and polymer also confirmed by the FTIR studies.

2.3 Formulation of Buccal patches

2.3.1 Solvent casting method:

The buccal patches containing prochlorperazine maleate was prepared by solvent casting technique. In this, Coating a sheet of release liner with an organic solvent allows for the co-dispersion of all patch ingredients, including the drug. Then, the patch [circular casting film] was die-cut to form patches of desired size and shape [8,9,10].

***Preparation of casting solution*:** Casting solution was prepare by dissolving HPMC & Chitosan in Distilled water with occasional stirring & kept for 24 hr to get a uniform dispersion of the solution in a beaker remove air bubbles.

API was added under constant stirring. After that add Propylene glycol, Citric acid into solution and then stir the solution for 1 hr. to get uniform viscous solution.

***Casting of matrices*:** For the formulation of buccal patch, The uniform dispersion of the casting solution on the petri dish. Petri dish was maintained at level position & dried the patch in oven at 40^0C.

***Backing Membrane*:** Ethyl cellulose (5%w/v) was dissolved in Acetone & Isopropyl alcohol (6:4). To this propylene glycol (40% w/w of polymer) was added as a plasticizer. This solution was spray(spraying rate 1 mL/min.) on one side of patch. This patch was allow to dry, After drying patch was wrap into aluminum foil and kept in desiccator**.**

2.4 Evaluation Tests of Buccal Patches

2.4.1 Weight uniformity:

An electrical weighing balance was used to calculate the individual weight of 2 patches from each batch. Then Patches' mean weight standard deviation was determined. Patches should have a weight that is essentially consistent. Making ensuring a patch has the right number of excipients and API is helpful [11].

2.4.2 Thickness:

Vernier callipers were used to determine the thickness of the patch. Five locations, including the centre and four corners, were used to measure the patch, and the mean thickness was computed. It was determined that there should be no more than a 5% variation in patch thickness. This is crucial in order to ensure uniformity in the patch's thickness, which is directly tied to the consistency of the drug content [12].

2.4.3 Surface pH Measurement:

The surface pH of the prepared buccal patch was determined to check the possible irritation potential of the patches to the mucosa. The test patch was put in a petri dish, soaked with 2ml of phosphate buffer pH 6.8, and allowed to sit for 30 minutes. After putting the electrode of the

pH meter into touch with the formulation's surface and giving it a minute to equilibrate, the pH was recorded. For each formulation, an average of three determinations were made[13].

2.4.4 Swelling index:

One key element determining adherence is the bio-adhesive polymer's degree of swelling. The polymers have a tendency to absorb water and swell. Thus, To investigate the patch's hydration qualities, a swelling index research was conducted. Separate patches were weighed (initial weight=W1), then they were put in petri plates with 5mL phosphate buffer pH 6.8 and let to swell. After 90 minutes, each enlarged patch was weighed separately (Final weight = W_2). Swelling index of each system was calculated using the following formula [10,14]:

$$\text{Swelling Index} = \frac{W2-W1}{W1} X\ 100 \text{ …..(2)}$$

2.4.5 Folding endurance:

To understand the elasticity of the patch during storage and handling, folding endurance of the patch is crucial. The ability of a patch to fold repeatedly at the same location until it breaks was evaluated. The folding endurance value is the number of times a patch can be folded without breaking. The precise figure of folding endurance was determined by counting how many times the patch could be folded in the same position without breaking. The folding endurance of prepared patches was measured in triplicate and average with SD was calculated [11].

2.4.6 Tensile strength:

The highest stress that may be applied to a strip specimen before it breaks is its tensile strength. Tensile strength was tested using specially made tensile strength measuring apparatus. The apparatus consists of a pan that was filled with weights. Between the two clips was positioned the patch whose tensile strength is being measured. It was observed how long the patch was at first. until the patch cracks, weights were put to the pan. The tensile strength can be calculated using the formula [15].

$$\text{Tensile Strength} = \frac{[Break\ Force]}{a\ X\ b} X \frac{[1+\Delta L]}{L} \text{……(3)}$$

Where ,

a is the thickness of the film b is the width of the film

ΔL is the length of elongation

L is the length of the film.

2.4.7 Drug content uniformity:

Each strip carrying 5 mg of the drug was sliced and dissolved in 10 mL of pH 6.8 phosphate buffer solution with constant stirring in order to ascertain the amount of drug in the created batches of formulation. Using Whatmann filter paper, the solution was filtered, and 1mL of the filtrate was then diluted to 50mL with the same buffer in a volumetric flask. In order to quantify the absorbance, a UV spectrophotometer was used at 255 nm [16].

2.4.8 Water permeability test:

One patch from the each formulation were weighed (W_1) and exposed to the 75 % relative humidity by using the Potassium chloride crystals in desiccator for a period of 24 hours. Patch was then weighed again (W2). Water permeability is indicated by the increase in weight and it was calculated by the following formula [17]:

$$\text{Water permeability} = \frac{W2-W1}{W1}\ X\ 100 \text{…….(4)}$$

2.4.9 Percent moisture loss:

One patch from each formulation were weighed (W_1) were placed in desiccator containing silica crystal/ Calcium chloride for a period of 24 hours. Patch was then weighed again (W2). Percent moisture loss is indicated by the decrease in weight and it was calculated by the following formula [17]:

$$\% \text{ Moisture Loss} = \frac{W1-W2}{W2} X\ 100 \ldots\ldots\ldots(5)$$

2.4.10 Drug diffusion studies:

Drug diffusion studies were carried out of the prepared patches by using Keishary chein diffusion cell with phosphate buffer 6.8 using dialysis membrane for a period of 6 hours. The cell membrane was mounted on a diffusion cell in between the compartments for the donor and the receptor. The membrane had the buccal patch attached to it. The pH 6.8 phosphate buffer was placed within the receptor compartment. The fluid was maintained at 37±2° and stirred continuously at 100±2 RPM. Aliquots of 1ml were collected at predetermined intervals for 6 h and suitably diluted, filtered through 0.22 µm filter and analysed by UV spectrophotometer. Same Phosphate buffer pH 6.8, 1 ml was replaced in the receptor medium to maintain the sink condition [18].

2.4.11 Bio-adhesion time:

By measuring the amount of time needed for the patches to separate from goat buccal mucosa, the patch's *In vitro* residency period was examined. The test was carried in disintegration apparatus using 500 ml phosphate buffer pH 6.8 maintained at 37°. While the mucosal side was facing up on the surface of a glass slide, the goat buccal mucosa was secured by tying with thread. Phosphate buffer solution was used to moisten the mucosa (pH 6.8). The patch (1 cm^2) was moistened with the same buffer, applied to the goat buccal mucosa, and allowed to move up and down such that it was completely submerged in and out of the buffer solution for one minute. The average of three readings was recorded along with the duration it took for the patch to separate from the mucosal surface [19].

2.5 Stability Studies

On prepared patches, stability studies were carried out to evaluate their stability with respect to their physical appearance, drug diffusion, drug content, thickness & folding endurance after storing them at 40^0C±2^0C/75%RH±5%RH for 28 days. Samples were withdrawn at 0,7,14,27 & 28 days [22].

2.6 Results and Discussion

2.6.1 Pre-formulation Studies of Prochlorperazine Maleate:

The sample of prochlorperazine maleate was received as a gift sample from Yarrow Chem Products. The sample of prochlorperazine maleate was analyzed for the various organoleptic & physiochemical properties. The sample possessed similar colour, odour, taste and texture as given in IP (Indian Pharmacopoeia). The melting point of prochlorperazine maleate was found to be 201-204^0 C which is in close vicinity to the literature value. The FTIR spectrum (Figure 01) of the drug shows the peaks which is concurrent to the structure of prochlorperazine maleate: 3015 (CH alkene group), 2974(CH_3 Stretching), 2872 (CH & CH_2 Stretching), 1694 (C=O Stretching), 1357 (CH aliphatic group), 1219 (C-C plus C-O). From the qualitative solubility test of prochlorperazine maleate it was found that the drug is freely soluble in

methanol & phosphate buffer pH 6.8 respectively and sparingly soluble in distilled water. The quantitative solubility of prochlorperazine maleate was found to be 2.15,1.54 & 0.013 mg/mL in methanol, phosphate buffer pH 6.8 & distilled water respectively. The partition coefficient of prochlorperazine maleate was found to be 4.07 in phosphate buffer pH 6.8.

The absorption maxima of prochlorperazine maleate in methanol, phosphate buffer pH 6.8 & distilled water was found to be 255 nm respectively. The calibration curve was prepared in methanol, phosphate buffer pH 6.8 & distilled water and obtained a straight line shows in Figure 02. The drug and polymer mixture was analyzed for 4 weeks and there no change was obtained in physical properties, FTIR peaks & absorption maxima of drug shows in figure 01 and table 02.

2.6.2 Evaluation of Buccal Patches

Formulations F1, F2, F3, F7 & F8 containing HPMC E-15 as a polymer was not formed because of the less quantity of polymer used in F1, F2 & F3 formulations and too much quantity of polymer used in formulations F7 & F8.

Also, formulations F9, F10, F11 & F12 containing chitosan as a polymer was not formed because of the chitosan was not dissolved properly so proper patch was not formed by using this polymer.

So, only F4, F5 & F6 formulations was selected for the further evaluation studies.

The evaluation parameters results are listed in table no. 2.

2.6.3 Release/ Kinetics pattern of F4, F5 & F6 Formulations [21]

The acquired data were fitted into several kinetics equations of zero order in order to analyse the mechanism of drug release kinetics of the buccal patches.Calculation of the regression coefficient was done & kinetic model graphs were created using the appropriate data are shown in Figure 03.

2.6.4 Stability studies

The stability study's findings showed that the drug closely conforms to the suggested stability standard. The statistics reveal that neither a substantial physical change nor a significant chemical change has occurred, indicating that the formulation will retain its potency and quality for the duration of its shelf life. The stability data is showed in table no. 3. The diffusion study was done after the storage period & the difference was showed in figure 04 & table 04.

2.6.5 Determination of Similarity Factor [20]

Buccal patches of formulation F4 was selected for the stability studies. For the determination of the similarity factor between before and after storage diffusion data of the F4 formulation. The US-FDA placed emphasis on determining the degree of similarity between in-vitro diffusion tests of various formulations. As implied by the name, it places a focus on the similarity of two comparative formulations. According to US-FDA, a similarity factor of 50 to 100 is generally considered appropriate. It can be determined by using the formula:

$$\mathbf{f2= 50.\ log\{[1+1/n\ \sum_{t=1}^{n}.\ (R_t - T_t)^2]^{-0.5}.100\}}$$

where,

n is the number of dissolution sample time

R_1 and T_1 are the individual or mean reference and test diffuse values at each time point.

F2 = 100 when two profiles are identical. An f2 value of 50 is produced by an average difference of 10% across all recorded time points.

The f2 value was found to be 72.8 which is more than 50 which indicate a close similarity between both the diffusion profile.

CONCLUSION

From the above evaluation test formulation F4 is selected as best formulation because the *In-vitro* diffusion of the formulation F4 was obtained 71.5 % in 6 hours it is more than the other formulations. The drug content of the best formulation was obtained 99.99%, folding endurance is 185 times.

No significant changes were observed on physical characteristics, drug content and on drug release of patches after keeping the patches for one month at 40 ± 2°C and 75 ± 5% RH. So, it was concluded that the prepared patches were stable under these stress condition.

It was concluded from the current experiment that creating buccal patches might be an inventive and promising method of delivering prochlorperazine maleate with better oral bioavailability. Thus, the drug administered as buccal patches should benefit patients experiencing nausea and vomiting, improve patient compliance, and provide a reliable method of preventing nausea and vomiting.

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Table no. 1: Different compositions of buccal patches containing HPMC E-15 & Chitosan

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Prochlorperazine Maleate (mg)	5	5	5	5	5	5	5	5	5	5	5	5
HPMC E 15(mg)	50	100	150	200	250	300	350	400	-	-	-	-
Chitosan(mg)	-	-	-	-	-	-	-	-	100	200	300	400
Ethanol (mL)	10	10	10	10	10	10	10	10	10	10	10	10
Propylene glycol(mL)	25	25	25	25	25	25	25	25	25	25	25	25
Citric acid(mg)	10	10	10	10	10	10	10	10	10	10	10	10
Mannitol(mg)	5	5	5	5	5	5	5	5	5	5	5	5
Tween 80 (mL)	5	5	5	5	5	5	5	5	5	5	5	5

Table 3: Evaluation data of F4 formulation during storage period

Time (days)	Real Time(30^0C/65%RH)				Accelerated(40^0C/75%RH)			
	Physical Appearance	Thickness (mm)	Drug Content (%)	Folding Endurance	Physical Appearance	Thickness (mm)	Drug Content (%)	Folding Endurance
0	Transparent	0.60	99.99	185	Transparent	0.60	99.99	185
7	Transparent	0.60	98.94	184	Transparent	0.60	98.52	181
14	Transparent	0.60	95.87	185	Transparent	0.60	94.83	180
21	Transparent	0.60	93.78	182	Transparent	0.60	91.75	178
28	Transparent	0.60	90.75	180	Transparent	0.60	90.14	175

Table 3: Evaluation data of formulations F4, F5 & F6

Evaluation parameters	F4	F5	F6
Weight variation(mg)	62.5 ± 1.351	75.2 ± 1.231	80.14 ± 1.167
Thickness (mm)	0.64 ± 0.04	0.68 ± 0.04	0.75 ± 0.05
Surface pH	6.7± 0.01	6.7± 0.02	6.8± 0.01
Swelling index (%)	18.12± 0.08	19.57± 0.06	22.80± 0.06
Folding endurance	185 ± 4.041	178 ± 3.512	176 ± 4.482
Tensile strength (kg/mm^2)	1.814± 0.030	1.431± 0.016	1.234± 0.013
Drug content (%)	99.99 ± 0.360	96.88 ± 0.321	97.13 ± 0.201
Water permeability (%)	3.51 ± 0.321	3.87 ± 0.141	4.32 ± 0.201
Moisture loss(%)	7.17 ± 0.030	7.70 ± 0.016	8.10 ± 0.023
Bio-adhesion Time(hours)	1.10 ± 2	1.12 ± 4	1.15 ± 4

Table 4:

Time(hrs)	Cumulative % drug diffused	
	Before storage	**After storage**
0	0.00	0.00
1	15.12	15.02
2	24.87	23.67
3	32.46	29.83
4	46.24	44.76
5	63.15	58.75
6	71.51	69.51

Diffusion data before and after storage

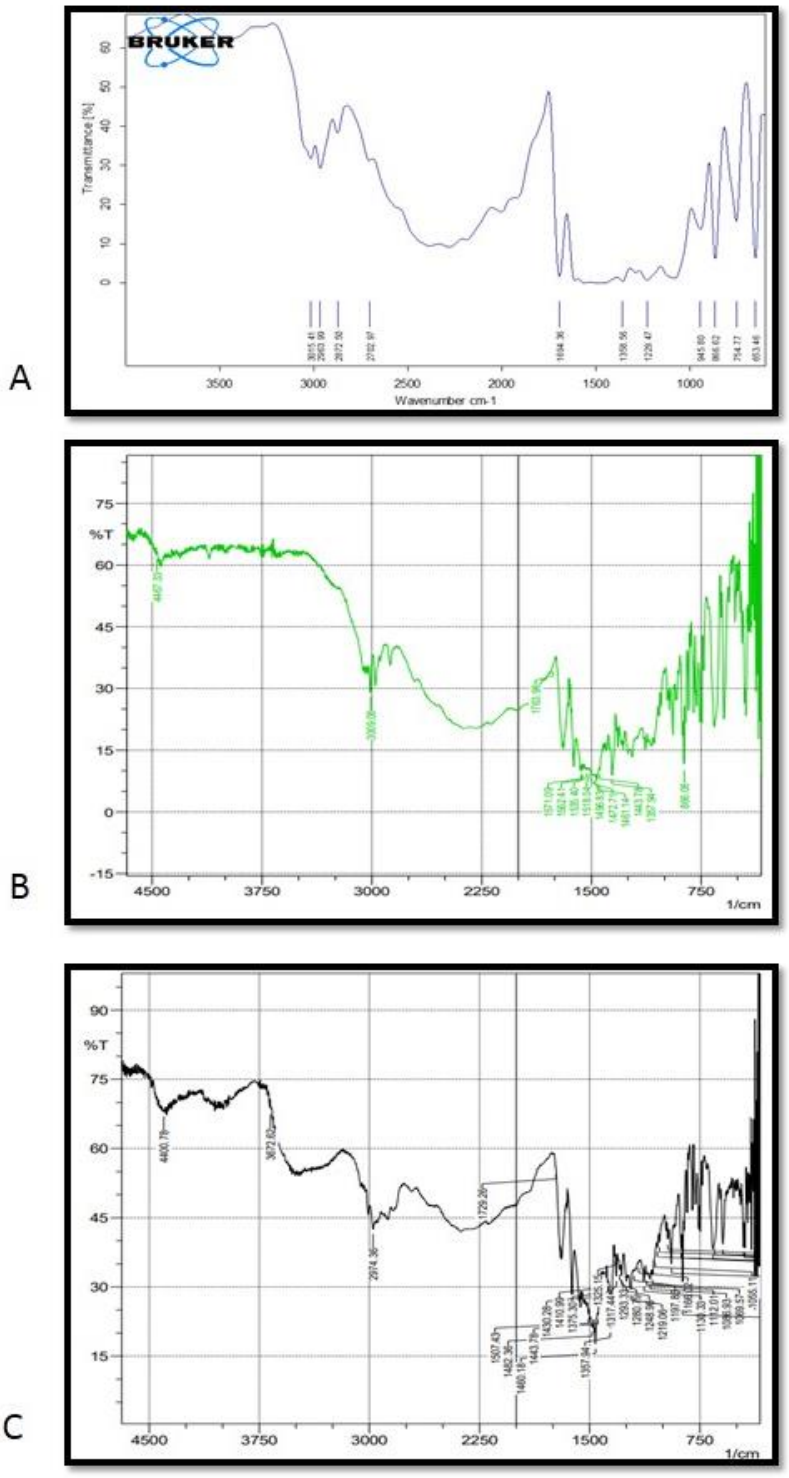

Fig 1: FTIR spectrum (A) Prochlorperazine maleate (B) Drug + Chitosan (C) Drug+ HPMC E15

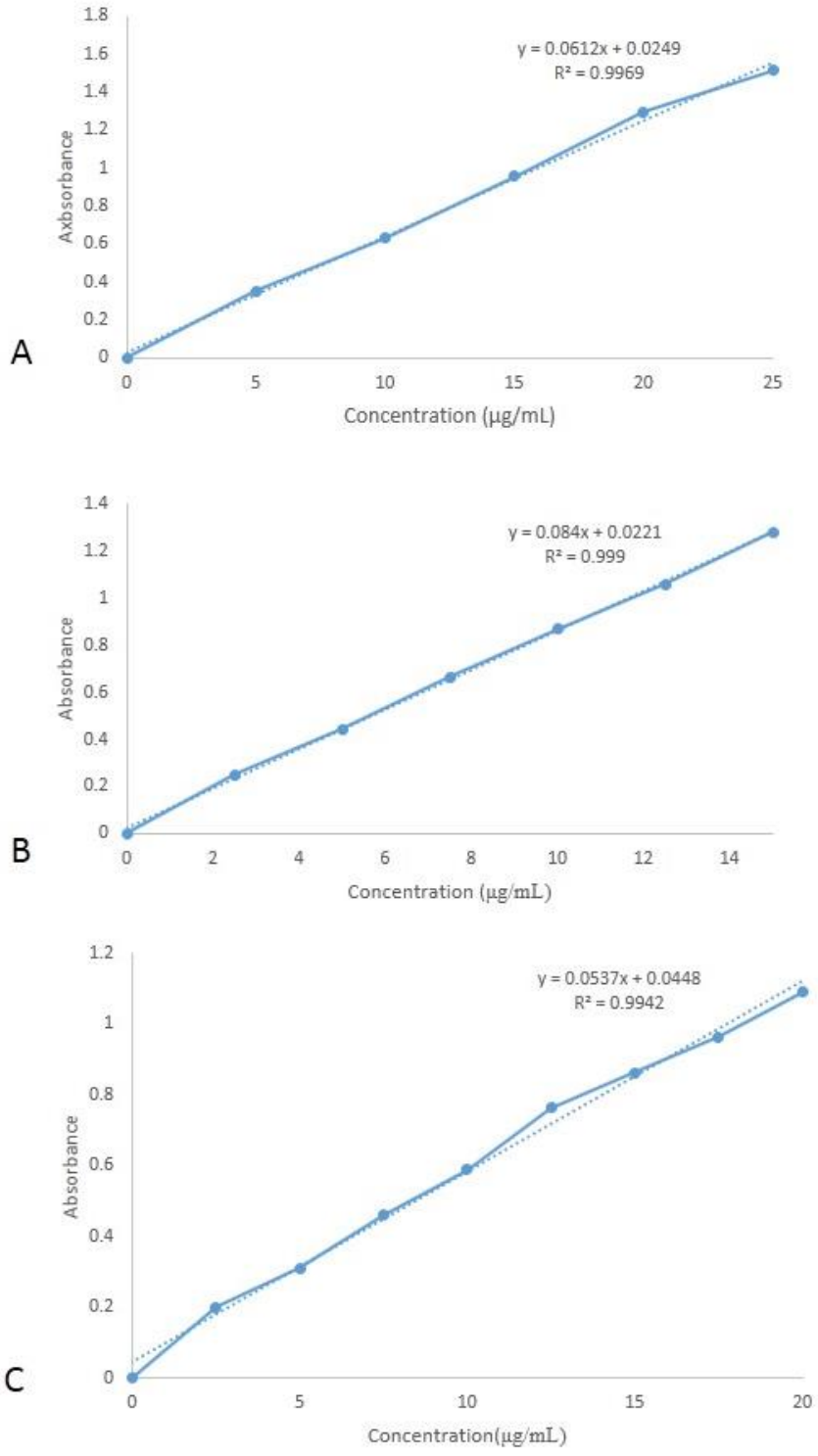

Fig 2: Standard plot of Prochlorperazine maleate (A) in Methanol (B) in Distilled water (C) in Phosphate Buffer (pH 6.8)

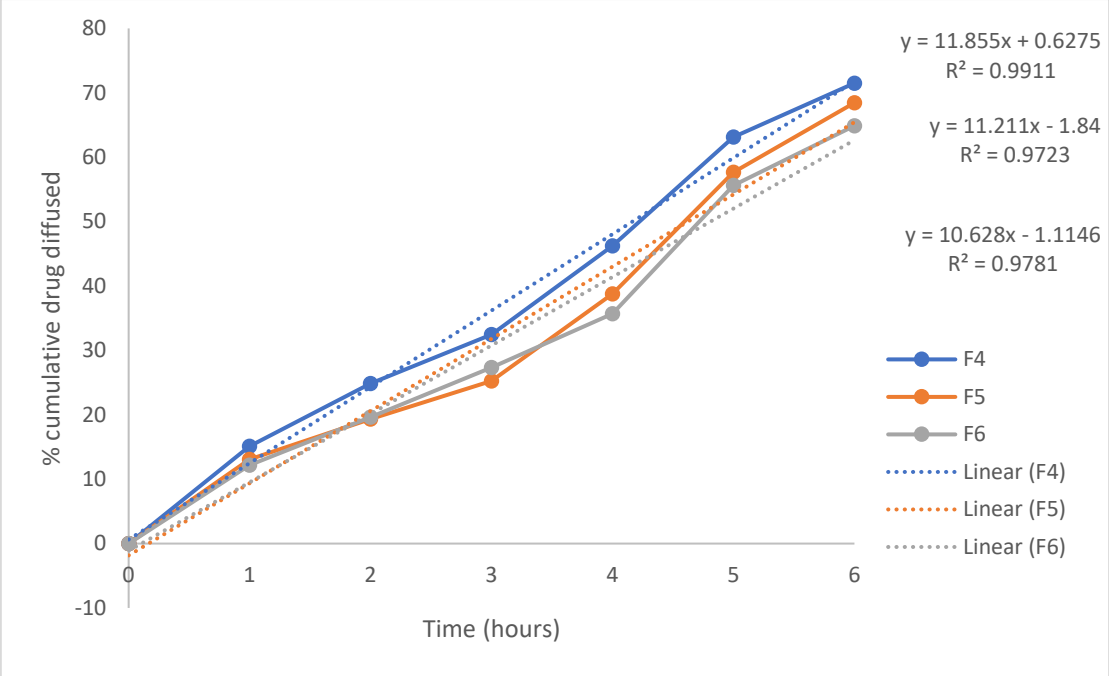

Fig 3: Zero Order Release of Formulations

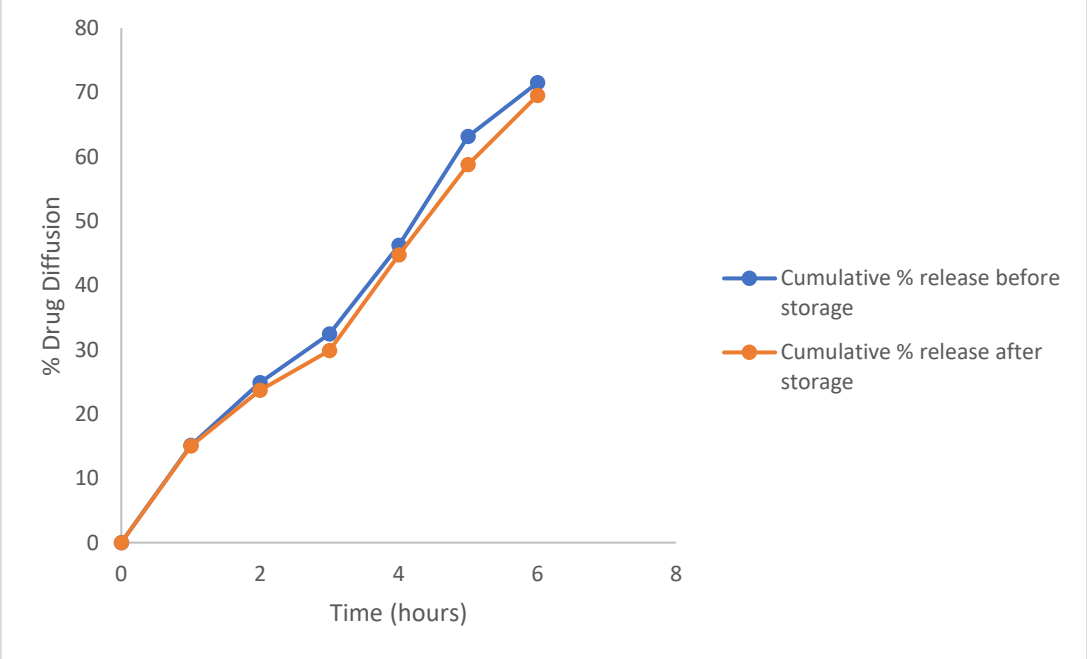

Fig 4: Diffusion of formulation F4 before and after storage