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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF GLYCOPYRROLATE

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Abstract: The main aim of the present work was to formulate fast dissolving oral film of Glycopyrrolate. Glycopyrrolate is an anticholinergic medication with a quaternary ammonium structure. It is a potent controller of Drooling observed in children affected with clebral plasy and has low oral bioavailability. This drug also undergoes first-pass metabolism. To overcome all these problems fast dissolving oral films were prepared which helps to improve the bioavailability of drugs. Oral films dissolve fastly along with drugs and mostly all drug absorbs through oral mucosa in the systemic circulation. Oral films were prepared by the solvent casting method. Pullulan and PEG 400 were optimized by using central composite 3 factor, 2 level design based on drug release, and thickness of films. A total of thirteen batches were prepared from which batch containing 50% Pullulan, 20% PEG was found to be best. Oral films of the optimized batch were disintegrated within 14 sec and show 85.60% drug release. The optimized film was further evaluated for drug content, folding endurance, pH values, disintegration time, percent elongation and physical appearance.

Keywords **- Poor saliva control, cerebral palsy, anticholinergic, drooling, glycopyrrolate, pediatrics, sialorrhea**

I. INTRODUCTION

The oral delivery industry accounts for approximately 52 percent of the overall drug delivery market; there has been a significant interest in development of modified release oral dosage forms. But there are some commonly associated problems while administration of drugs orally like minimizing the risk of partial loss of API due to tablet or capsule crushing or imprecise liquid administration which results in dosage inaccuracy and drug therapy overdosing or inefficiency [1-3].

In order to overcome these issues, fast dissolving drug delivery systems are garnering a lot of attention. These films dissolve quickly in the mouth, releasing the flavour [4–6]. Many drug companies have been diverted by recent technical breakthroughs to explore new opportunities in this technology to give fast, accurate dosing that is expected to boost compliance, particularly among children and also it can improve the dissolution of the poorly soluble drug [7–9].

There is no need for water or measuring required as the dose of medicine is swallowed. Absorption of drug by oral mucosa into systemic circulation is an attractive approach because it is highly vascularised and hence highly permeable. As a result, fast dissolving films have become a preferred oral dosage form for a variety of medications, as their large surface area allows for rapid disintegration and hence improves patient compliance.

In the formulation of Mouth dissolving film of Glycopyrrolate, Pullulan and PEG400 use as film-forming polymer and plasticizer. Pullulan is a natural polysaccharide made up of repeating maltotriose units that works well as a film-former, resulting in a heat-sealable film with good oxygen barrier properties [10, 11]. Sodium Sachharin is used as a sweetening agent and water is used as a vehicle.

Glyopyrrolate (GLP) is an anticholinergic compound having quaternary structure. Glycopyrrolate has been recently approved by the Food and Drug Administration to treat sialorrhea in children aged 3–16 years cause due to neurological issues [13]. Solubility of Glycopyrrolate is low in water. The low aqueous solubility of the drug decreases the bioavailability of the drug Glycopyrrolate is an anticholinergic (antimuscarinic) agent, competitively inhibiting acetylcholine receptors on peripheral tissues. These receptors inhibit the salivary glands which helps to stops the parasympathetic nerve impulses by indirectly reducing the rate of salivation [14,15]. Drooling or sialorrhea is common in children, particularly in those with cerebral palsy and other neurodevelopmental disabilities. Excessive drooling can make it more difficult to care for children with chronic neurological problems by isolating patients and their families socially and causing secondary dermatitis and infection. Hence, based on the rationale of the proposed research work, the aim of present investigation was to develop and formulate pullulan based fast dissolving films of Glycopyrrolate by solvent casting method for direct drug absorption into the systemic circulation via transmucosal lining. The proposed formulation has the potential to improve compliance and offers a number of competitive benefits over its marketed oral dosage forms.

II. Materials and methods

Materials:
Glycopyrrolate was obtained from Harman Finochem Ltd, MIDC Industrial Area, Chilkalthana, Aurangabad, Maharashtra India. Pullulan was obtained from B.R.D.H. Scientific Suppliers, Nagpur. All other ingredients were of analytical grade and were not altered in any way.

Preparation of mouth dissolving film:
The mouth dissolving film of Glycopyrrolate was prepared by the solvent casting method. In which Pullulan used as film former. PEG 400 as a plasticizer and flavouring and sweetening agent was added [16].

Method of preparation of drug loaded fast dissolving films:
By dissolving the necessary amount of pullulan in sufficient quantity of distilled water (70%), a polymeric solution (Solution A). With constant stirring, a specific amount of medication, polyethylene glycol, and other excipients were dissolved in the remaining water (30%). (Solution B). With continuous stirring, Solution B was slowly added in polymeric solution A. For defoaming, the final solution was set aside for 30 minutes. After defoaming, solution kept aside for 30 min. and then poured in petri plate and dried at room temperature for 24 hr [17, 18]. The film was carefully flaked off and cut into pieces of the desired shape and size after being cast in a petri plate. The composition of formulation as per the factorial layout as shown in table no 2.

Drug Excipient compatibility study:

Fourier Transform Infrared Spectroscopy Study: FTIR Spectrum of API of Glycopyrrolate and the other excipient use in the preparation of Glycopyrrolate MDFs was recorded. By using FTIR spectroscopy, the sample was analyzed by KBr method. About 10 mg of a formulation is mix with dried KBr in equal quantity. The mixture properly mixes using mortar and pestle. After that, the powder was scanned across the frequency range.

Formulation of Mouth Dissolving Film of Glycopyrrolate:
Optimization by Central Composite 3^2 Factorial Design: A 3^2 randomize full factorial design used in the present study. In this design, 2 factors were evaluated each at 3 levels, and experimental trials of all 13 possible combinations were performed. The film Thickness and Drug release (%DR) were selected as the dependent variable. Two independent factors the concentration of polymer and Plasticizer were set two-level; each factor coded as -1 and+1, respectively.
The actual formulation design of Mouth Dissolving Film of Glycopyrrolate according to full factorial design (3^2) Layout as shown in table no 2.

Table No. 1: Formulation factors, concentration, and levels

Factors	Polymers		Plasticizer	
Concentration (%)	40	50	5	20
Levels	-1	+1	-1	+1

Table No. 2: Formulation layout as per the factorial design

Batch No.	Polymer (%) Pullulan	Plasticizer (%) PEG 400
F1	40	20
F2	45	1.8934
F3	40	5
F4	45	12.5
F5	50	20
F6	45	12.5
F7	37.9289	12.5
F8	45	12.5
F9	50	5
F10	45	12.5
F11	45	23.1066
F12	45	12.5
F13	52.0711	12.5

III. Evaluation parameter of mouth dissolving oral film:

Morphological properties: MDFs were usually tested for properties such as homogeneity, color, transparency, and odor. All the formulation is stored at room temperature. The films were packed in aluminum pouches [19].

The thickness of the Film: The thickness of the film was measured by micrometer screw gauge with a range of 0-10 mm and revolution 0.001 mm Anvil of the thickness gauge was turned and the film was inserted after making the pointer was set to zero. The estimation was completed in triplicate [20,21, 22].

***In-vitro* disintegration study:** There are several official methods available for the disintegration test. The required size of the film (2cm Diameter) place in a beaker containing 10ml distilled water. The disintegration time was noted which was the time when the film started to break or disintegrate. All studies were completed in triplicate for each batch [23, 24].

pH Value: The pH value was determined by dissolving film in 10ml distilled water [25]. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min [26]. All determination was performed in triplicate. Film must have a nearly uniform pH value.

Folding Endurance: Folding endurance of the film is required to study the elasticity of the film in the course of storage and handling. The folding endurance of the film was determined by repeated folding one film at the same place till break. These consider revealing good film properties. A film (2cm) was cut evenly and repeatedly folded at the same spot until it breaks. All determination was performed in triplicate [27, 28, 29].

Percent elongation: At the point when stress is applied to the film test extends and alluded to as a strain. Generally, elongation of the film increase as the plasticizer concentration increases. The percentage elongation of the film was determined by the following formula [20, 30].

Percentage elongation = Increase in length of strip/ Initial length of strip × 100

Drug Content uniformity: Drug content was determined by dissolving the film of 4cm^2 dissolved in 100ml water to get 20µg/ml solutions. An aliquot of 2 ml sample was withdrawn and diluted to 10ml with water. Then the solution was filtered through Whatman filter paper and analyzed by UV-Spectrophotometer at ʎ max of a drug. For each batch of the film, content uniformity tests were performed in triplicate [20, 30].

***In-vitro* Dissolution Studies:** Glycopyrrolate Mouth dissolving films drug release studies were determined by Franz Diffusion Cell Apparatus having external diameter is 3 cm, internal diameter is 2.8cm, the height of diffusion cell apparatus is 8cm and volume is 30ml. The receptor compartment maintained at 37ºC was continuously stirrer at 100rpm. Sample of 1ml was withdrawn at a predetermine time interval over a 30min and replace with an equal volume of the dissolution medium equilibrated at the same temperature. The drug concentration of the withdrawn sample was determined by UV Spectrophotometer at ʎ max of a drug. All studies were carried out in triplicate for each batch of the film sink conditions were maintained throughout the study [31].

Table No. 3: Evaluation Parameter of MDFs of Glycopyrrolate

Formulation Batches	Thickness of Film (mm)	pH Value	Percent Elongation (%)	Folding Endurance	DRUG Content (%)	Disintegration Time (Sec)	Drug Release (%)
F1	0.145	6.85	2.32	110	90.1	11	65.23
F2	0.15	6.48	1.10	111	96.8	12	67.73
F3	0.16	6.55	2.32	114	95.5	13	68.23
F4	0.16	6.55	2.32	114	95.5	13	68.23
F5	**0.19**	**6.88**	**2.46**	**135**	**99.6**	**14**	**85.60**
F6	0.14	6.68	1.26	104	97.8	10	62.47
F7	0.16	6.55	2.32	114	95.5	13	68.23
F8	0.16	6.55	2.32	114	955	13	68.23
F9	0.16	6.55	2.23	114	95.5	13	68.23
F10	0.13	6.82	2.63	108	96.3	11	49.36
F11	0.18	6.76	1.32	130	97.9	13	78.30
F12	0.17	6.46	3.54	122	90.0	11	75.5
F13	0.20	6.20	2.68	128	85.5	10	91.19

IV. Result and Discussion:

Characterization of drug:

Physical Appearance:

Glycopyrrolate was checked visually for colour, odour, nature and solubility. The results are summarized in table: Table.no.4

Table no. 4: Physical appearance of Glycopyrrolate

Sr.No.	Physicochemical Properties	Glycopyrrolate
1	Colour	White
2	Odor	Odourless
3	Nature	Amorphous Powder
4	Solubility	Water, Ethanol

Melting point:

Melting point of Glycopyrrolate was found to be 193°C.

Table no. 5: Melting Point of Glycopyrrolate

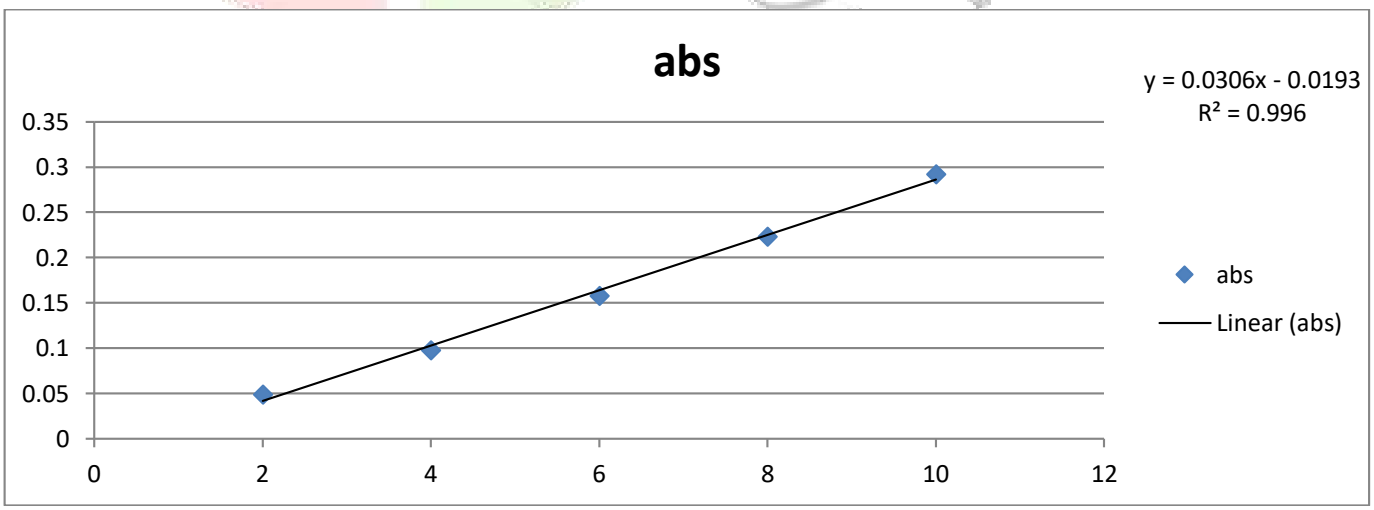
Sr.No.	Observed Melting Point	Mean	Therotical Melting Point
1	191°C		
2	193°C	193°C	192-195°C
3	195°C		

Calibration curve of drug:

The standard curve of Glycopyrrolate in distilled water using UV-spectrophotometer (Shimadzu UV 1700) was estimated. The absorbance show at 222 nm was noted down as show in table no. 6. The standard plot of absorbance against concentration plotted as show graph no. 1.

Table no. 6: UV Spectroscopic data of various concentrations

Concentration (µg/ml)	Absorbance at 222 nm
2	0.049A
4	0.098A
6	0.168A
8	0.223A
10	0.292A



Graph no. 1 – Calibration Curve of Glycopyrrolate

Optimization of independent variables:

Results from preliminary studies suggested that 5–45% pullulan and 20–30% PEG 400 causes stickiness in films. The films made with a composition of 55–95% pullulan and 5–15% PEG 400 were nonuniform. However, films made with concentration of pullulan at 40–55% and PEG 400 at 15–20% were non sticky, uniform and clear. Based on the findings, polymers with a pullulan content of 45–55 percent and a plasticizer content of 15–20 percent were chosen for further development.

Optimization of dependent variables:

Response 1: Thickness

ANOVA was used to determine the significance ($p < 0.05$) of the model and individual response parameters. The effect of independent factors on the measured responses was investigated using surface response plots and contour plots. The quadratic model of F-value 149.54 implies the model is significant. The effect of different independent variables on thickness was shown in the surface response plot and contour response plot (Fig. No. 1).

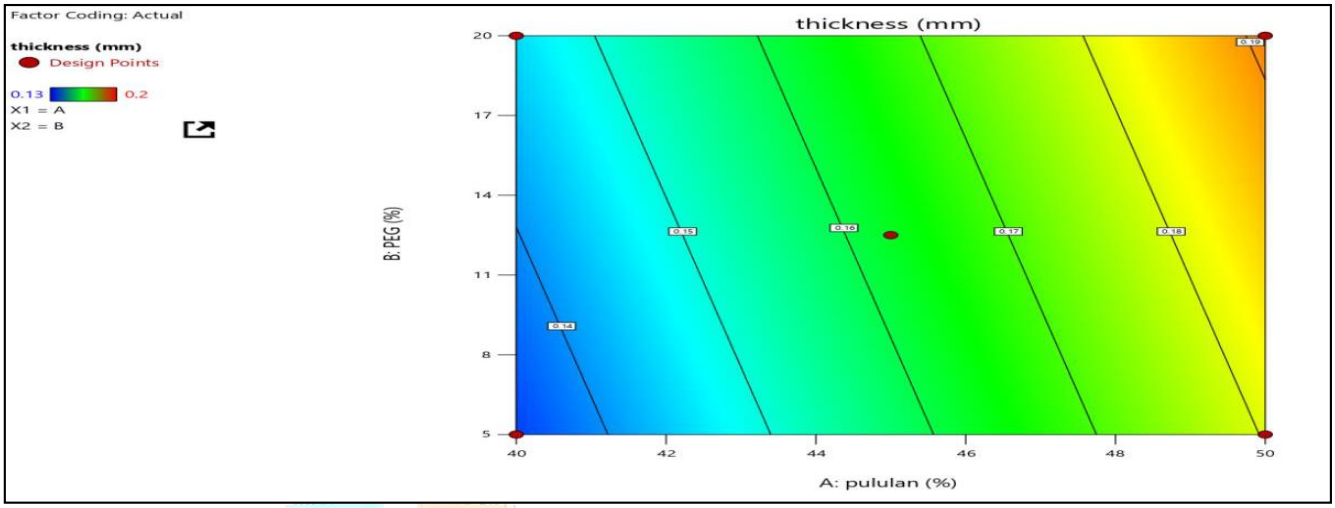


Figure No. 1: Counter plot of effect of concentration of polymer and plasticizer on thickness of film

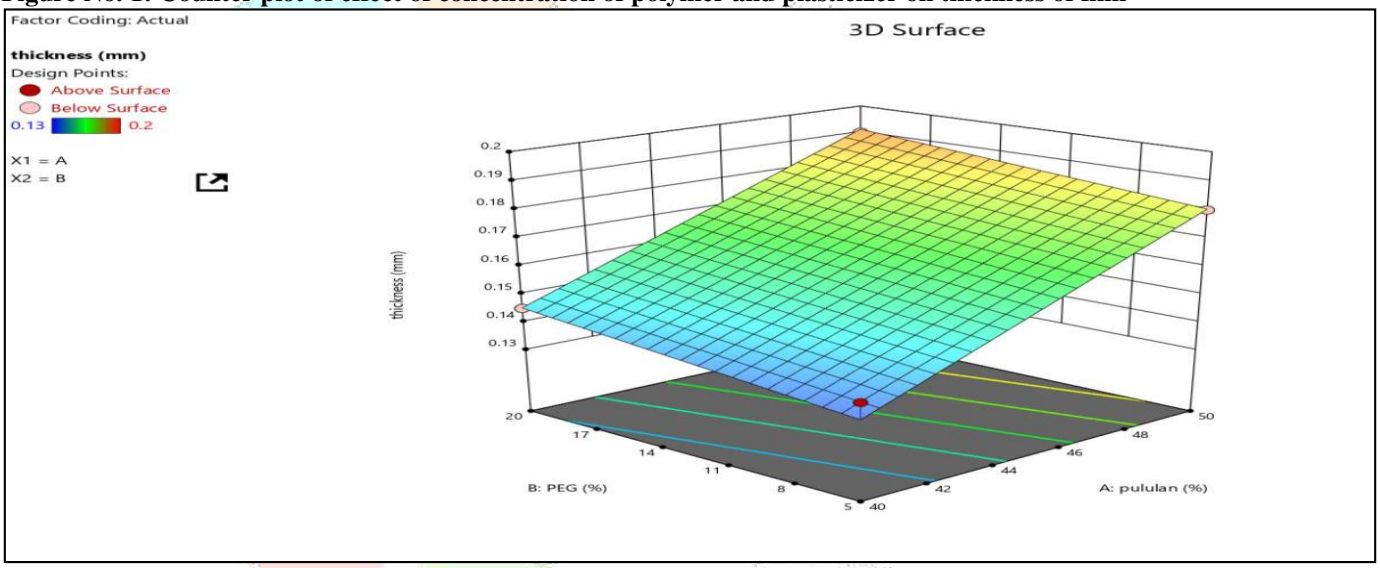


Figure No. 2: 3D Graph effect of concentration of polymer and plasticizer on thickness of film

Response 2: Drug release

After ANOVA estimation, the quadratic model of F-value 38.58 implies the model is significant $p < 0.0500$. The contour plot and surface response plot in Fig. No. 3 and 4 showed the effect of different independent variables on drug release.

As the amount of plasticizer and polymer in the film increases to 45–55%, the drug release increases. When concentration of polymer

reached to 55% then drug release was decreases since drug remains

inside the matrix of polymers.

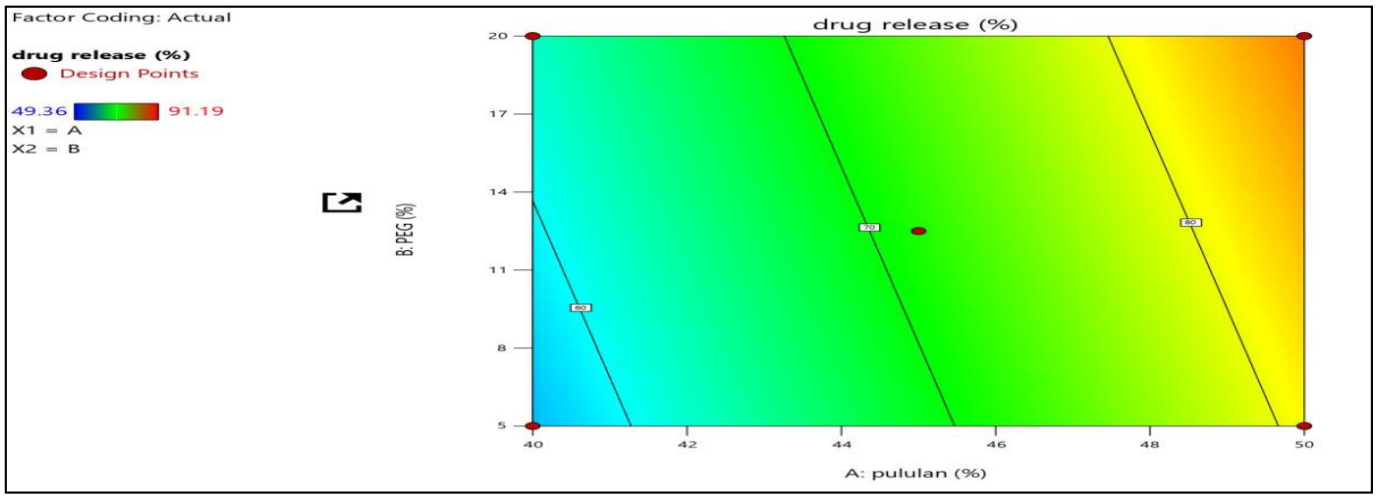


Figure No. 3: Counter plot of effect of concentration of Polymer and plasticizer on Drug Release

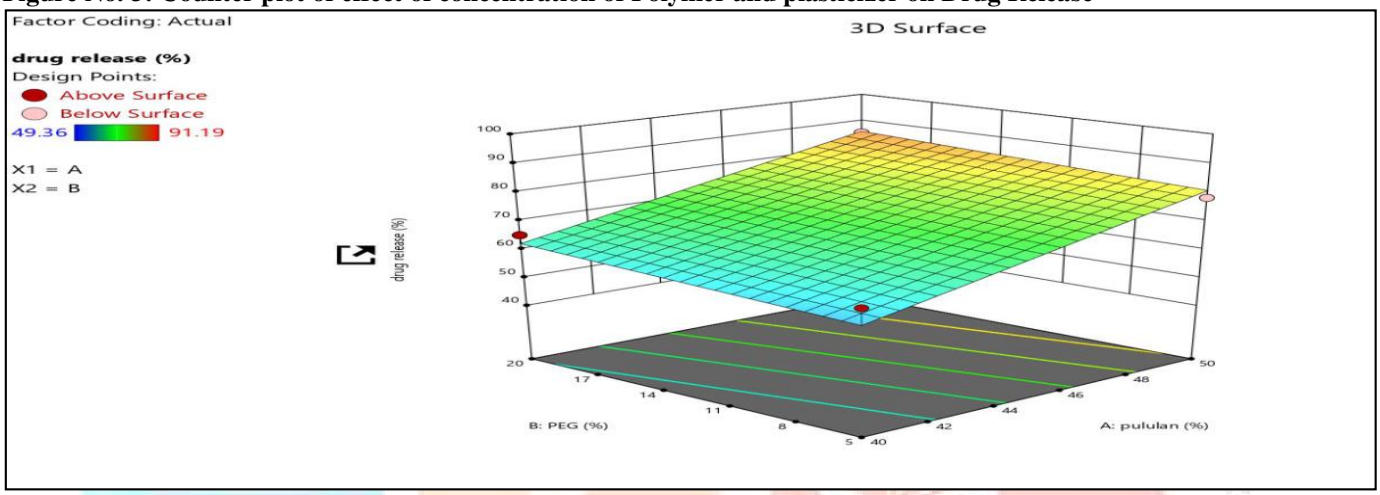


Figure No. 4: 3D Graph for Effect of Concentration Polymer and Plasticizer on Drug Release

Stability studies:

The stability study of the Glycopyrrolate was done in stability chamber. Stability studies were carried out at 40 0C / 75 % RH for 2 months and following result were obtained. On storage the optimized film did not show any significant change in appearance, weight loss, disintegration time and % drug content. From these results it was concluded that, formulations containing Glycopyrrolate is stable and retained their original properties. The results of disintegration time, drug content and transparency are shown in the Table, which indicates no alteration after storage.

Table No. 7: Result of Stability study of Optimized Batch F5

Sr. No.	Parameter	Initial	30 Days	60 Days
1	Thickness (mm)	0.19	0.19	0.19
2	pH Value	6.88	6.88	6.88
3	Disintegration time (sec)	14	15	15
4	Drug Content (%)	99.6	99.5	97.1
5	Drug Release (%)	85.60	85.5	86.4

CONCLUSION:

The aim of present research work was to formulate MDFs by employing the 3^2 central composite design and evaluate different formulations of fast dissolving films of anticholinergic drug Glycopyrrolate to achieve faster drug release to control chronic drooling in children. This study shows that it is possible to formulate mouth dissolving films of Glycopyrrolate with the intention of obtaining better therapeutic efficiency with increasing bioavailability and improving patient compliance. Compatibility of Glycopyrrolate with polymers was confirmed by FT-IR studies.

Pullulan is used as film forming polymer, PEG 400 is used as plasticizer. Sodium saccharin used as a sweetener will successfully mask the bitter taste of the drug Glycopyrrolate.

Because of the elasticity of the polymer, tensile strength, percentage elongation, and folding endurance of the films increased as the polymer concentration was increased. As more fluid is required to wet the film in the mouth, the mouth dissolving time and disintegration time of the films increased as the polymer concentration increased. The drug is evenly distributed throughout the film, according to a content uniformity study. Present study reveals that the formulated films showed satisfactory film parameters. It can be concluded that, Mouth dissolving film containing Glycopyrrolate can be prepared by solvent casting method. And it can be a potential novel drug dosage form for children.

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