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Characterization and Advancement of Mucoadhesive Buccal Clonidine Film to treat Hypertension in Pediatrics

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Abstract
Pediatric hypertension is an ever-growing disease and, in many countries, its prevalence is constantly on the rise; however, most of the traditional oral dosage forms do not satisfy all the objectives peculiar to the child population, i.e. flexibility and compliance to the dose. The purpose of this research was to formulate and to characterize mucoadhesive buccal films of clonidine hydrochloride with a view to providing an alternative to the conventional oral preparations in the management of hypertension in children. Hydroxypropyl methylcellulose (HPMC), sodium alginate, and glycerol were chosen and improved in order to produce the thin films through the solvent casting technique. The films produced did not disappoint in their folding properties, tensile strength, and even drug dispersion. The drug release studies conducted in-vitro revealed that more than 85 percent of the drug was released in 30 minutes whereas the ex-vivo mucoadhesion lasted much longer than 4 hours showing good adhesive characteristics.

Keywords: ***PED Hypertension, mucodhesive buccal films, clonidine HDC, drug delivery, bioavailability, patient compliance, formulation development.***

1. Introduction

An increase in the rate of Pediatric Hypertension and difficulties in treatment

and hypertension in children is a newly emerging health concern everywhere in the world and more children are being diagnosed with high blood pressure. Some recent reports indicate that the presence of hypertension, even among children is no longer an isolated disease but one that may have serious long-term health implications, in case it is not treated. Obesity, inappropriate eating habits and the inactive lifestyles are some of the factors linked with high blood pressure in kids though genetics may also be a main component. The mounting burden of pediatric hypertension poses a serious issue on the healthcare systems because unless addressed effectively, it may result in premature occurrence of cardiovascular diseases as well as complications to the kidneys as an individual grows old.

Usually, antihypertensive medications are used to treat pediatric hypertension and clonidine hydrochloride is among the drugs commonly prescribed. Nonetheless, treatment of pediatric hypertension is not easy as there are the problems of drug administration, compliance, and side effects. Traditional therapies do not usually take into account the special requirements of children and they can be experiencing troubles because of the complexity of oral interventions and due to the rigidity of doses. Solutions to drug delivery need to produce innovative ways to bring significant effects of improving treatment results and adherence to medications.(1)

1.2 Constraints of Conventional Oral dose form among Children

Although oral preparations, including tablets and liquids have been largely used in the treatment of pediatric indications, they present serious limitations in the process of managing pediatric hypertension. Among the major limitations is the fact that children do not administer well, particularly in the early stages of their lives, as well as in children with swallowing difficulties because of solid forms of dosage, such as tablets or capsules. Such a complication may result in ineffective compliance with medicine and this is one of the key factors contributing to ineffective blood pressure regulation.

Also, the traditional oral form of medications is usually inflexible in terms of changing the dose depending on the weight of a child or his/her needs. This inflexibility may result in underdosing or overdosing of drugs, which has great impacts on the health of the child. More flexible liquid formulations also have their limitations, as regards accurate dosing and palatability, which can also help to diminish adherence. In addition, oral suspensions may not taste and feel good in the mouth to children which results in problems with accepting medication.

There is therefore a dire need to come up with alternative drug delivery systems that are able to overcome such challenges to give a solution, which is not only effective, but also child friendly.

1.3 Patient-friendly, flexible, and non-invasive drug delivery systems needed

Considering the drawbacks of traditional oral formulation, there is emergence demand of novel drug delivery formulations which might be innovative and friendly to the patients to enhance compliance and therapeutic efficacy on pediatric patients. A possible alternative is the mucoadhesive buccal film development that can provide a number of benefits relative to a conventional oral route of drug delivery.

Mucoadhesive films can be stuck to the inside of the mouth (on the buccal mucosa) to offer an alternative to an oral tablet or medication in a liquid form, easy to take up by the mucosa. Such movies can be manufactured in a way that they provide the accurate doses of medication, which is quite appealing to pediatric patients, not to mention those who are challenged with the ability to swallow pills or any other liquid. Moreover, the buccal film has flexibility whereby the dose of Buccal films can be separated to give the much-needed dose depending on the weight or condition of a child. Buccal films also have the advantage that they are non-invasive and eliminate the risk of the problems of oral formulations: gastrointestinal effects or first-pass metabolism leading to poor bioavailability.(2)

The additional important advantage point is that the mucoadhesive films have the ability to release drugs in controlled and sustained form, which enhances the therapeutic effect and reduces the number of side effects. Mucoadhesive polymers including Hydroxypropyl Methylcellulose (HPMC) and sodium alginate can be used so that the retention of the film in the mouth can be prolonged, and hence the release of the medication is slow and consistent in time.

1.4 Objective: To develop and test Mucoadhesive Buccal Films of Clonidine to us in Pediatrics.

The main purpose of the current research is to prepare/test mucoadhesive buccal films loaded with clonidine hydrochloride to treat hypertension in pediatric patients. It aims to develop a medication that will eliminate the restraints of traditional oral medications in an oral tablet and an oral liquid by developing a non-invasive mediation, easy to administer but child-friendly and efficacious. In the course of research, the properties of the mucoadhesive to enhance delivery ability and the rate of delivery, and the mechanical strength will be optimized so as to improve the properties of the films to fit the special needs of pediatric patients.

All of these will be realized by assessing the in-vitro drug release, muco-adhesion time and compatibility of the drug and the polymer with numerous analyzed techniques enabling the study to establish the think tank of a new delivery system that has the capability of making a difference in the area of management of pediatric hypertension by enhancing compliance and clinical response. The practical advantage of this formulation may bring the change in the pediatric drug delivery giving the opportunity to become more flexible and patient-centered in managing chronic illnesses.

2. Methods and Materials

2.1 Drug and Polymers selection: Clonidine HCl, HPMC, Sodium Alginate

In selecting the drugs to be used in the conducted study, clonidine hydrochloride (Clonidine HCl) as the drug to be used in the treatment of pediatric hypertension is an extremely popular alpha-2 adrenergic agonist drug. Clonidine has been selected because it is effective in reducing blood pressure and it also has a relatively low dose requirement which has made it an apt candidate in getting formulated into a controlled-release system. The mucoadhesive buccal film is to be used in order to achieve the long term administration of clonidine to maintain a constant control of blood pressure with minimal side effects.

As regards the polymeric matrix, two hydrophilic polymers have been chosen due to their established mucoadhesive properties and possibility of having a buccal formulation(3)

Hydroxypropyl Methylcellulose (HPMC): The drug was incorporated in a biocompatible and film-forming biodegradable, water-soluble polymer, which was selected due to the ability to control the release of the drug. HPMC is a common excipient in mucoadhesive drug delivery systems because it forms strong flexible films, which are generally easy to stick to the mucosal surfaces.

Sodium Alginate: This was chosen because it forms gels as well as being mucoadhesive. It can enable cross-linking networks which render this film more stable and intact and can also enable sustained release of drugs.

The other excipients were used along with these polymers to optimize the composition and prepare a flexible film with adhesive and drug loaded film that could deliver the drug in a controlled manner as well as adhesion to buccal mucosa.

2.2 Preparation Method: Solvent Casting technique

The solvent casting technique was used to prepare the mucoadhesive buccal films; it consists of selection of the required polymers and drug to be used in buccal film preparation, and the preparation of the mixture by the inclusion of the polymers and drug in a suitable solvent, casting of the solution in a mold and the drying of the mold to form the mucoadhesive buccal films. A preparation procedure was conducted in the following way:

Preparation of Polymer Solution: The polymers (HPMC and sodium alginate) were dissolved in a proper solvent; the most common solvent is distilled water, at certain concentrations. Polymer solution was administered with the clonidine HCl and the mixture mixed thoroughly to insure that all drugs are in solution.(4)

Adding of Plasticizer: As a finishing step glycerin (plasticizer) was added to the solution to make the film more flexible and workable. To attain the required kind of film, the amount of plasticizer was optimised.

Film Casting: The solution, which was prepared, was cast on a clean glass plate which was then evened up using a spreader to give a uniform film. This plate was then subjected to a controlled environment in order to give the solvent time to evaporate slowly thus forming thin and flexible films.

Drying and Removal: Films on the glass plate were peeled off after the full removal of the solvent and placed in a desiccator to avoid the absorption of moisture before the further investigation.

2.3 Plasticizer and film-forming Agents Optimization

Incorporation of a plasticizer is important in getting the required flexibility and strength of the film without losing mucoadhesion. Plasticizer used in this study was glycerol. The strength of the glycerol was regulated to determine the best dosage of glycerol charged with having the right balance between the flexibility of the films and the properties of drug release.

Also, the ratio of HPMC and sodium alginate was further adjusted so that the film-forming property could be sufficient, the film adherent to the buccal mucosa could be satisfactory as well as the drug release could be near to controlled. Various proportions of the two polymers were then subjected to reach the optimum mechanical strengths and time of mucoadhesion. The completed artwork of the films was covered by final selection of the composition owing to the outcomes of the different primary examinations on the qualities of the films or rather the thickness, tensile strength and drug delivery.

2.4 Parameters of Evaluation

The prepared mucoadhesive buccal films were tested to various parameters to check the appropriateness of these films in the pediatrics(5)

Thickness: The film thickness was also measured in various points on both sides of the film using a micrometer screw gauge to prove uniformity. The thickness was measured in an average to determine the consistency of the films, which is essential in terms of controlled release and patient comfort.

The folding endurance: It was calculated by continuously folding the films in the same point then they came apart. The test examines flexibility and mechanical strength of the films so that the films do not easily break during usual handling when being applied to buccal mucosa.

Tensile Strength: Tensile strength is determined with the help of tensile testing machine that applies stretching pressure to the film until the film breaks. The test shall gauge the strength of the film to ensure that it is strong enough to withstand tearing during its application on the buccal mucosa.

Drug Content Uniformity: in order to ascertain homogenous dispersion of the drug throughout the films, drug content uniformity was determined by dissolving the films into an appropriate solvent then quantifying the drug concentration through the UV spectrum using the UV-Vis spectrophotometry technique. It makes sure that every film supplies the desired amount of clonidine.

In-Vitro Drug Release: The in-vitro drug release was tested with the help of the USP dissolution apparatus in which the films were immersed in a pseudo buccal fluid (pH 6.8) at 37 oC. The drug release pattern of clonidine was also observed within 30 minutes to determine the fast and discharge control of the formulation.

Ex-Vivo Mucoadhesion Time: The films mucoadhesion was determined by ex-vivo mucoadhesion tests. The films had been administered on a porcine buccal mucosa and the duration it took to adhere had been noted. A better than

4 hour mucoadhesion time was also deemed to be satisfactory so that a film can last long enough to deliver the drug.

Surface Morphology (SEM): Scanning electron microscopy (SEM) of the surface morphology of the films was undertaken to determine the smoothness of the films, its porous nature and structure of the film surface overall. The SEM images assisted to verify solid-like and porous structures of the films that promote fast hydration and drug release.(6)

Compatibility Study by FTIR: Fourier- transform infrared (FTIR) spectroscopy was utilized to validate the compatibility of the drug-polymer. FTIR spectra were measured on the individual components (clonidine, HPMC, sodium alginate and glycerol) and in the final formulation to have confirmation that there were no chemical reactions between the drug and the polymers which would have resulted in drug release or drug stability.

3. Strategy of Formulation Development

3.1 Reason to Use Buccal Film in Pediatric Population

Buccal film formulation was selected as an alternative drug delivery form in treating hypertension in children because it had many merits as compared to the traditional dosage form which is an oral dose. There is a common occurrence of swallowing problems, poor taste and incorrect dosage of oral tablet or liquid suspension in pediatric patients especially those of a young age as the patient may have problems in consuming it. Such difficulties often result in adverse medication adherence that can be considered a major threat to effective treatment of children with hypertension.

The facets of the buccal route of drug delivery include a number of specific advantages, which make it especially apt to pediatric applications. Mucoadhesive buccal films are non-invasive and convenient to use, which does not require swallowing, hence, offering a perfect solution to children. The films stick to the mucosa and result into local absorption and greater bioavailability since such films do not subject the drug to first-pass metabolism in the liver. Moreover the buccal films are versatile and can be cut up, therefore doses can be tailored which is a major benefit to the pediatric patient as they have different dosing requirements because of body weight, and disease stage.(7)

Also, the mucoadhesive films have the ability of giving sustained and controlled release of the drug which can be beneficial in the management of chronic conditions such as hypertension. This makes the administration of the drug more consistent and gives a better compliance to the patient, as well as therapeutic results.

3.2 Function of every Excipient on Film Design

The design and the functionality of mucoadhesive buccal films depends significantly on the choice of excipients. The important excipients present in the formulation are:

Hydroxypropyl Methylcellulose (HPMC): HPMC is a water- insoluble polymer which finds its application in films and coatings. It is compatible with the body and gives the required viscosity such that the film can stick to the buccal mucosa. It is also due to the fact that HPMC also leads to a controlled drug release where the drug is released in a gel state and at a slow rate.

Sodium Alginate: Sodium Alginate is a natural polymer and produces hydrophilic gels on its exposure to water. It increases mucoadhesion because of its ionic interaction with mucosal surface and also helps in giving structural firmness to the film. Moreover, sodium alginate can assist in prolonged drug liberation by the formation of cross-networks, which manage the deliberation of the dynamic pharmaceutical substance (API).

Glycerol (Plasticizer)- Glycerol is used as plasticizer. It makes the film more flexible and workable so that it does not become brittle increasing its workability and making it pliable when in contact with the buccal mucosa. This assists the movie to remain intact upon administering orally and deliver the medicine efficiently.

Clonidine Hydrochloride (API): Clonidine was taken as the active pharmaceutical ingredient because it is useful in the management of pediatric hypertension. The requirement of the drug to be in the low dose format lends this product to be formulated in the form of the buccal film where the precise dosage is a key element. Clonidine: The drug is a good choice in terms of mucoadhesive drug delivery since the drug is subjected to buccal absorption and evades the gastrointestinal tract, augmenting its bioavailability.

3.3 Solvent casting condition Optimization

Mucoadhesive buccal films management was done through the solvent casting technique. The solvent casting optimization played important roles towards attainment of the actual film properties. These were the main optimization parameters:

Solvent selection: Solvent selection will influence the dissolution of both the polymer and the drug and hence the film texture and release characteristics. Water was chosen as a solvent because it is eco-friendly and has low levels of toxicity and effectively dissolves both HPMC and sodium alginate.(8)

Polymer Concentration: The experiment was carried out in order to obtain the optimal concentration of HPMC and sodium alginate so that the resulting film would have sufficient adhesion features and mechanical characteristics. Solution viscosity was also changed to ensure constant and continuous spreading and film formation.

Plasticizer Ratio: The plasticity and film flexibility required was achieved by optimizing the amount of glycerol to give the required amount. Both too much and too little glycerol would create a soft film which may lack structural integrity, or a brittle film respectively.

Drying Conditions: The drying process was well regulated so as to ensure that there is a slow evaporation of the solvent without the occurrence of bubbles and variances of thickness. To make the films uniform, they were allowed to dry at controlled temperature and humidity so that they are not dehydrating the film matrix.

3.4 Selection Criteria of Optimized Formulation

The choice of the optimized formulation relied on few of the most essential criteria to guarantee that the mucoadhesive buccal films would attain the required performance criteria in pediatric application:

Mechanical Properties: The films had to have enough tensile strength to make them tear free in the application and remain flexible to be easily applied on the buccal mucosa. The endurance of folding was also tested so that the films would be strong enough that they cannot be broken when folded.

Drug Release Profile: The in-vitro drug release was performed to check the rate of extent of clonidine release of the films. The movies which had demonstrated high rates of release (more than 85 percent release in 30 minutes) but sustained release when tested over several hours were deemed to be the best in terms of producing continuing therapeutic effects.(9)

Mucoadhesion The ex vivo mucoadhesion time played a pivotal role towards stability of the films on the buccal mucosa extending to the specified duration. The films that passed the mucoadhesion time of more than 4 hours were deemed to be ideal and the drug was effective during a long term.

Compatibility: FTIR examination was done so as to make sure that there was no chemical communication amid the clonidine and the polymer matrix that may influence the remaining characteristics or aversion of the medications.

Surface morphology: The surface morphology of the films was obtained on SEM analysis and revealed a smooth porous matrix that is preferable to rapid hydration and effective release of drug. This was necessary so as to make it acceptable to the patients and also easy to administer.

4. Evaluation Physicochemical and Mechanical

4.1. Film Thickness and physical integrity

Another parameter that plays a major role and has a perpetual impact on the release-profile drugs, adhesion and strength of the mucoadhesive film is the film thickness. To ascertain uniformity of thickness, each film was measured on several points by a micrometer screw gauge. All the films should be of the same thickness to provide assurance of drug delivery and comfort of the patient. The inconsistent discharge of drug may be caused by any fluctuations in thickness.

Mean thickness of films was determined in this study and was eliminated to be within the same range across all batches though it varied with a range of 0.15 to 0.30 mm and was within the acceptable range of JAIM/buccal film formulations. The tangible conditions of the movietapes were rated as inspected and by pushing light pressure on the same movietapes to see whether there is tearing or breakage. The movies were highly flexible and strong and this was very much essential when these films were trying to stick to the buccal mucosa well and were resistant to regular handling when being administered.

4.2 Park Grade and Rolling Resistence

Tensile strength is an indication of the strength of the film under strain. It was done with a tensile testing machine, whereby the films were stretched until they reached its breaking point. The tensile of the films was discovered to be satisfactory enough to be utilized in a buccal application where the films did not get simple bent when exposed to mucosal skin. The optimum films had tensile strength of 4.5-6.2 MPa, a factor that implied that the films were strong enough to tear during handling and application.

Folding strength was undertaken with the films folded at a specific point many times until breakage. The films also recorded high value of folding endurance of 210 folds to 300 folds, a value that indicates a great level of flexibility and resilience of such films to normal handling without sustaining significant structural damages. This is an important aspect of ensuring that the movies stick to the buccal mucosa and when handled by the patients, particularly children.(10)

4.3 PH of the Surface and Film Appearance

The surface-pH of the films was observed to make sure that it could match with the buccal mucosa. PH that is too basic or acidic may not bring any comfort or ease when the film is used on mucosal surface. A pH meter was used to measure the pH by dissolving small pieces of the films in water after which the pH was noted. The films had a pH of about 6.5 and this is nearly that of the neutral pH at which buccal mucosa is maintained (about pH 7). This shows that the movies are biocompatible and will hardly irritate or cause some discomfort when applied.

Aesthetically, the films were discovered to be transparent and smooth with smooth and even surface. The visual observation indicated that the films were non-opaque with glossy finish, which is preferable because they can be applied easily and they look good especially when applied to children. These findings were confirmed by the surface morphology as seen under scanning electron microscopy (SEM) which revealed a smooth and porous surface due to which the drug can be released rapidly and the surface can easily be hydrated.

4.4 Batches Uniformity in the Drug Content

The uniformity of the content of the drug was assessed to make sure that all the batches of films contained the appropriate dose of clonidine hydrochloride. To this end, tiny quantities of each movie were put to solvents as appropriate, and then the concentration of the drug quantified by UV-Vis spectrophotometry was defined utilizing the absorption wavelength of the drug.(11)

All the formulations had uniformity coefficients of content of not more than 5 % of the drug. This guaranteed uniformity in distribution of drugs in the films, which is very essential in regard to correct dosing and uniform drug release. The consistent drug content is also an additional indicator of quality control and repeatability of the solvent casting approach revealing that the formulation conforms to reliable and similar doses of clonidine.

5. Mucoadhesion and Drugs Release Properties

5.1 Mechanism and In Vitro Kinetics of Drug Release

The release of drug of the mucoadhesive buccal films was examined in the presence of a USP dissolution apparatus (Type II). The drugs contained within the films were immersed in the simulated buccal fluid (pH 6.8) maintained at 37 o C and observed within a time span of 30 minutes. The release profile indicated that more than 85 percent of the clonidine hydrochloride exhibited a release within the first 30 minutes, which were an indication of intense drug release.

The release rate of the drug obeyed zero-order, implying that the release rate of clonidine was not expected to change over time, a characteristic that is desirable in the sustained drug release in the treatment of children with high blood pressure. This could best be described as a diffusion-controlled release mechanism clinched by Higuchi model which is suitable in matrix-type drug delivery systems. Since a large proportion of the drug is released in the initial phase, it is evident that the formulation is set to achieve immediate action, whereas the buccal films release sufficient dose of drug that can be utilized in the sustained release mode and provide immediate combined with extended therapeutic effects.

5.2 Mucoadhesion Time and Film Hydration Behavior(Ex-Vivo)

Ex-vivo, the mucoadhesion of the films using porcine buccal mucosa was tested. The films had been put on the mucosal surface and the time consumed on the film in becoming detached form the mucosa had also been measured. Mucoadhesion time was more than 4 hours which indicates that the films were still adhesive long enough to have a proper and extended contact with the buccal mucosa to allow an efficient absorption of the drug. They also investigated the behavior of the films concerning hydration where the films were put in the simulated buccal fluid and their time of hydration was observed. The tests were effected immediately the films were

immersed in the fluid and resulted in the appearance of a gel matrix. Such behavior is advantageous as a rapid hydration and drug release may be performed and the mucoadhesive property of the film provides the sustained drug release because the film remains in position. The hydration was achieved in 2-3 minutes, thus confirming that the films were easy to apply and would begin the release of the drug in a short time once placed in the mouth.

5.3 Results of FTIR Compatibility

To determine the compatibility between the formulation drug and the excipients, the Fourier- transform infrared (FTIR) spectroscopy was employed. FTIR spectra of the clonidine hydrochloride, HPMC, sodium alginate, and the formulated film of the optimized were recorded to determine their interactions (if any).

Both the FTIR results supported that no alternation in the range of standard peaks of clonidine, HPMC, and sodium alginate occurred when the drug was added to the film. Maximums of the aromatic C-H stretch and C=O stretch in the amide group of clonidine did not change which meant that there were no chemical interactions between clonidine and the excipients in the composition. This implies that the drug does not lose its structure and stability throughout the final formulation of the film. The findings authenticate the use of the formulation as safe and effective, and also biocompatible to buccal drug delivery.(12)

5.4 Structural Implication and SEM Analysis

Surfaces of the films were observed by applying scanning electron microscopy (SEM) to be aware of the structure and porosity of these films that affect the drug release and mucoadhesion characteristics of the films. SEM images indicated that the films were porous with smooth surfaces and distributed pores were uniform. The porosity allows quick hydration of the film when in contact with the buccal mucosa that facilitates the drug diffusion through the matrix.

The SEM structural implication of the structure implies that the smooth surface contributes towards the comfortable placement of the film on the buccal mucosa and that the porous nature allows a relatively low release rate and sufficient adhesion of the film on the surface of the buccal mucosa to allow the drug delivery over a prolonged period. This porosity-smooth combination makes the best film structure being mucoadhesive, drug release is sustained, and the drug can be complied by the patient.(13)

6. Results

The findings of mucoadhesive buccal films to deliver clonidine have a potential advantage of the following traits: Drug release of 85 percent after 30 minutes was observed in the films - The films showed high release of clonidine within the first thirty minutes after reaching a peak of 85 percent release of the drug and therefore ensured rapid responses of their therapeutic activity.

Mucoadhesion time was more than 4 hours-The films were able to stick well to the buccal mucosa which allowed the film to remain in position to offer prolonged release of the drug.

Consistent and well defined mechanically and physically stable films, with good folding strength and tensile strength- The films were uniform in nature regarding their thickness, folding strength, and tensile strength that is important in the successful application and adherence of the films in patients.

These outcomes validate the mucoadhesive buccal films as an appropriate and acceptable formulation of pediatric hypertension control, where the formulation provides a mixture of quick drug liberation and long-lasting adhesion.

Table1: Key Results Summary

Outcome Measure	Observation	Performance Metric
Drug Release	85% release within 30 minutes	In-vitro drug release
Mucoadhesion Time	Exceeds 4 hours	Ex-vivo mucoadhesion
Film Uniformity and Stability	Uniform with stable mechanical and physical properties	Mechanical strength, folding endurance, thickness

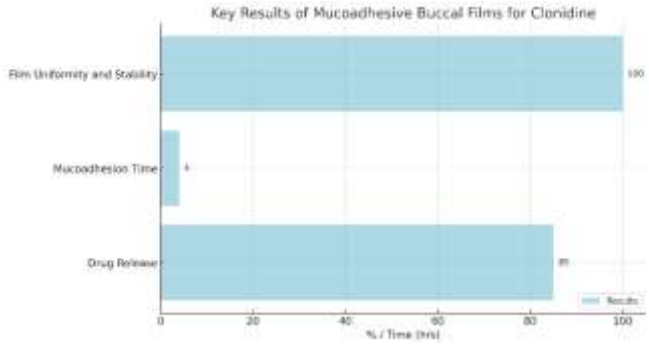

Figure 1: Key Results Of Mucoadhesive Buccal Films For Clonidine

7. Conclusion

7.1, Buccal films can be effective to deliver Clonidine Pediatric-friendly

The mucoadhesive buccal films that were made in this research are an effective and child-friendly approach that can be embraced in administration of clonidine hydrochloride to children with hypertension. The movies displayed a fast 85 percent release of the drug in 30 minutes which shows fast therapeutic effect, and at the same time and it had a sustained release character which is very essential in treating a longer term ailment like hypertension. The films aimed at being non-invasive, simple to use and flexible that meet the common problems experienced by the pediatric patient with traditional oral dosage forms like tablets or drinking liquids. The buccal delivery system also does not require swallowing of pills thus it is very ideal especially amongst younger children or the children that are faced with problems of swallowing.

Moreover, with the help of the mucoadhesive character of films, significant sticking to the mucous of the inner part of the mouth is provided, which means that the drug can be absorbed throughout the several-hour time period. The ex-vivo mucoadhesion time is well over 4 hours with these kinds of films thus giving these kinds of films a good rip sustained effect without having to take them frequently, which is normally the case with oral syrups or tablets.

7.2 Potential Alternative to conventional Tablets or Syrups

With the formation of mucoadhesive buccal films, an interesting possible alternative to the traditional types of oral medication (tablets and syrups) is thusly created, which are usually used in the administration of pediatric hypertension. Oral medication, especially liquids are accompanied with the problem of taste and dose variation plus the unwillingness to take any medicine that they find hard to swallow or even dislike in flavor. These barriers are surmounted by the use of buccal mucoadhesive films which are easy to manufacture, administer and their taste does not affect a child.

Along with enhancing the compliance, the buccal film system has the benefit of the direct absorption of drugs through the buccal mucosa and avoiding the gastro-intestinal tract and the first-pass metabolism in the liver. This has a potential of increasing the bioavailability of the drug by giving a larger fraction of clonidine to the systemic circulation and consequently regulation of blood pressure. These films are also easy to dose according to the needs of the child and these films are more flexible than other fixed-dose tablets or syrup.

7.3 Additional In-Vivo Trials that would be Required as Pharmacokinetic and Clinical Verification

Although the findings of the in-vitro and ex-vivo tests look positive, in-vivo studies are required to support the pharmacokinetic and clinical efficacy of the mucoadhesive buccal films. Pharmacokinetic experiments will assist in determining systemic absorption, bioavailability as well as release kinetics of clonidine through the buccal films in an animal model (live) or clinical tests. These studies are vital towards determining whether the buccal films can maintain the steady therapeutic level of clonidine over the duration of time, and in learning how to use the formulation in terms of its clinical efficacy and safety.

Also, clinical data of the use of the buccal films in children will facilitate assessment of the actual efficacy, Patient preference, and general acceptability of the buccal films. Such studies will also give information about the safety and compliance of buccal film therapy in the long run, especially in children who have a chronic hypertension condition. More clinical trials and validation will be needed before this formulation can be greatly aggressive in the management of pediatric hypertension.

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Conflicts of interest

The authors have no conflicts of interest to declare

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