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Nano-suspension loaded mucoadhesive mouth dissolving film of meclizine hydrochloride

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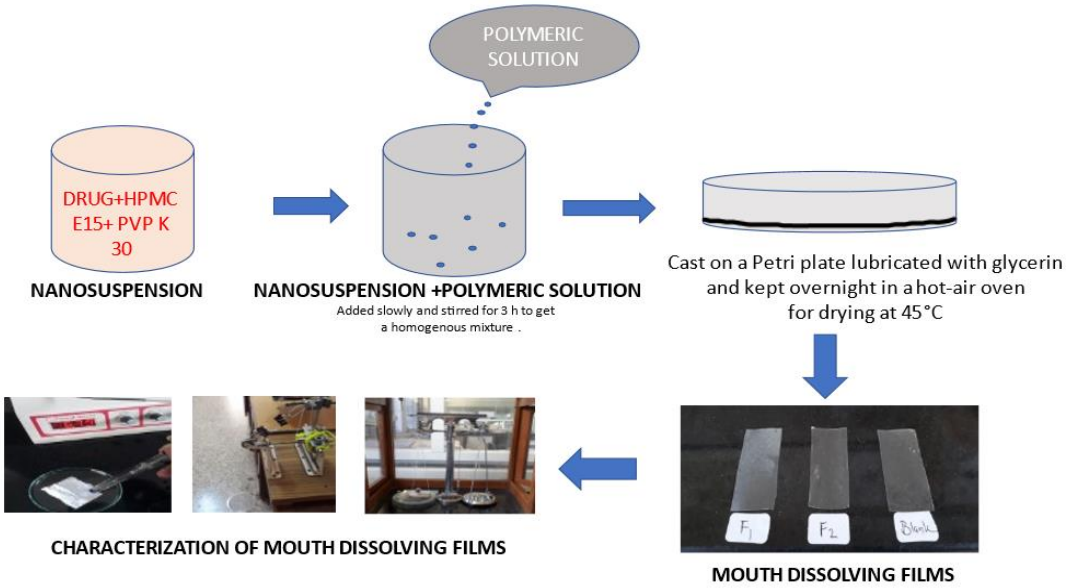
ABSTRACT

Meclizine Hydrochloride belongs to class H1 antagonist, antiemetic and anti-vertigo in nature, it is a Biopharmaceutical classification system (BCS) class II drug and is practically insoluble in water. The bottom-up approach was used in the formulation of nanosuspension in which methanol and millipore water was used as solvent and anti-solvent respectively, the stabilizers used for preparation were Polyvinylpyrrolidone K30 (PVP K30) and Hydroxypropyl Methylcellulose E15 (HPMC E15) which were found to be compatible with the formulation after Fourier Transform Infrared (FTIR) and Differential scanning calorimeter (DSC) studies. Mouth dissolving films were formulated by solvent casting method using glycerine lubricated petri dish and were kept for heating in a hot air oven at 45°C overnight. Characterization of nanosuspension-loaded mucoadhesive mouth dissolving films was done by evaluating various characteristics, the highest drug content was found to be 92.43±0.49% in Mouth dissolving film (MDF) 2. In-vitro drug release studies indicate that nanosuspension-loaded mucoadhesive mouth-dissolving film has a rapid drug release rate as compared to plain drug-loaded mouth-dissolving films and marketed tablet formulation.

Figure 1: Graphical abstract



Keywords: Nanosuspension, Meclizine Hydrochloride, Solvent casting, Mouth dissolving film.

INTRODUCTION

The oral route of administration is the most widely used route for drug administration for systemic and local effects because of its painless ease of administration, non-invasive and patient compliance. The intra-oral route for drug delivery is an attractive site as the oral cavity avoids drug degradation due to first-pass metabolism in the gastrointestinal tract. Nanosuspension can be described as a biphasic system made up of pure drug particles dispersed in an aqueous medium with a diameter smaller than 1µm. Because of their increased surface area and saturation solubility, nanosuspensions have a faster rate of dissolution and hence faster onset of action [1]. The objective of the current study is to prepare and evaluate Meclizine HCl mouth dissolving film in order to ensure rapid action with more therapeutic effect by improving dissolution while additionally considering patient compliance. Oral solid dosage forms are convenient for many drugs, but they might be difficult to formulate if the active ingredients have a low bioavailability or poor dissolution rate. Numerous methods have been developed to improve the drug's solubility and rate of dissolution in order to address these issues. Formulation of nanosuspension is simple and cost-saving used for both hydrophobic and hydrophilic drugs generating a physically stable product. Two widely employed processes for manufacturing nanosuspension are “bottom-up process technology” and “top-down process technology”. Bottom-Up process Nanoparticles can be set up from precipitation, micro emulsion, and dissolve emulsification method. Top-down process Nanoparticles are obtained by high-pressure homogenization and milling method [2]. Mouth Dissolving Films are oral solid dosage forms that dissolve when placed in the mouth without the use of water. In the elderly, pediatric, and dysphagia populations, mouth-dissolving films are being widely accepted as they are convenient and simple to administer. A mouth-dissolving film is novel approach and uses a very thin film, mostly made of plasticizer and polymer, that is intended to be placed anywhere in the oral cavity, even on the tongue. Within seconds, these films get hydrated and disintegrate inside the mouth cavity after becoming wet by saliva. In comparison to alternative mouth-dispersing drug delivery systems, such as orodispersible tablets, mouth-dispersing films are made in a continuous process on production-scale equipment at a relatively low manufacturing cost [3].

Mouth-dissolving films are monolithic matrices prepared by either solvent casting, hot melt extrusion, semisolid casting, or rolling method. The method of choice selected for carrying out this research work is solvent casting method. Solvent casting method gives better uniformity of thickness film with fine gloss and freedom from die lines, more flexibility and physical properties.[4,5]. Meclizine hydrochloride (MCZ HCL) is a first-generation antihistamine of the piperazine class drug, it is an H1 receptor antagonist and is used in the treatment of vertigo and motion sickness. It has a shorter half-life of 5-6 hrs. Meclizine hydrochloride is almost insoluble in water. It is used as an antiemetic/antivertigo agent, specifically in the prevention and treatment of motion sickness-related nausea, vomiting, and dizziness [6,7]. Chewable pills and orally disintegrating tablets of meclizine HCL that are currently in the market. Poor water-soluble drugs are allied to slower rate of absorption from oral route, so, there is a necessity to enhance the dissolution of these drugs to ensure maximum therapeutic utility of these drugs [18]. Mouth dissolving films of Meclizine Hydrochloride when placed on the tongue or in the oral cavity, immediately hydrates, adheres, and dissolves releasing their active ingredients in several directions to give a localized or systemic drug delivery. The goal of the current study is to prepare and evaluate a mouth dissolving film containing Meclizine Hydrochloride in order to ensure patient compliance and higher therapeutic efficacy. This will increase dissolution and provide a quicker onset of action and greater therapeutic effect.

MATERIALS AND METHODS

Meclizine Hydrochloride was obtained as a gift sample from Symed Labs Ltd Hyderabad and HPMC E5 LV, and HPMC E15 were gifted by Yarrow Chem Products, Mumbai. PVP K30, PVA, Sodium saccharine, Citric acid, Propylene glycol, Glycerol LR, and Methanol purchased from Hi Media Laboratories Pvt. Ltd, Mumbai. All other excipients and solvents obtained were of analytical grade.

Screening of polymers for formulation of placebo mouth-dissolving films

Screening of polymers was done to select the film-forming polymers which can be used in the preparation of nanosuspension by ultra-sonication assisted solvent anti-solvent technique and mouth dissolving film using solvent casting method. A sufficient quantity of film-forming polymer was soaked overnight in 30ml Millipore water. This polymeric solution was later stirred for about 2hrs without heating on a magnetic stirrer to get a homogenous solution. To this solution 10% v/v propylene glycol was added as a plasticizer. Another solution was made in which a sufficient quantity of sodium saccharine and citric acid was dissolved completely in Millipore water. Both the solutions were mixed to get a homogenous mixture at sufficient RPM to avoid bubble formation further this solution was cast on petri plate lubricated with glycerin and was kept overnight in a hot air oven for drying at 45°C. The films were cut in 2×4 cm^2 size and the superior sample films were further chosen to carry out its characterization. The smoothness, transparency, and homogeneity of obtained films were visually assessed. These films' flexibility and disintegration characteristics were assessed. By calculating the folding endurance value, the films' flexibility was evaluated [8]. Polymers were chosen for further formulation based on the findings. The used polymers must exhibit good hydrophilicity, quick disintegration, a pleasant mouth

feel, and appropriate mechanical qualities. The polymer should have excellent solubility in addition to enough physicochemical, mechanical, and permeability qualities. A film needs to have a high mechanical strength and adequate elongation and elasticity qualities in order to maintain its integrity against the internal and external stresses created during storage, especially when exposed to climatic conditions.

Table 1: Formulation table of placebo Mouth dissolving films

Polymers	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
HPMC E 5LV (%w/v)	2	3	4	5	-	-	-	-	-	-
HPMC E 15 (%w/v)	-	-	-	-	2	3	4	5	2	2
PVP K 30 (%W/V)	-	-	-	-	-	-	-	-	1	-
PVA (%w/v)	-	-	-	-	-	-	-	-	-	1
Propylene Glycol (%v/v)	10	10	10	10	10	10	10	10	10	10
Citric acid (%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium saccharine	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Millipore water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Characterization of blank mouth dissolving films

Characterization of blank placebo films were conducted by determining the folding endurance in which the precisely cut film of 2×4 Cm² size were repeatedly folded at same place till it breaks and number of times films can be folded without breaking it apart was taken as value of folding endurance and disintegration time of the formulated mouth dissolving films was was determined visually.

Preparation of Meclizine Hydrochloride Nanosuspension

The ratio of polymers used in the formulation of placebo mouth dissolving films were used in the preparation of Meclizine HCL Nanosuspension. Meclizine HCL nanosuspension was prepared by ultrasonication-assisted solvent anti/solvent technique [4]. Polymers were weighed accurately and kept to soak overnight in 30ml Millipore water to obtain lump-free polymeric solution. 175mg of Meclizine Hydrochloride was weighed accurately and dissolved in 5ml of methanol completely using a bath sonicator. The drug solution was added cautiously with the help of a syringe to polymeric solutions made up using stabilizers and surfactants like HPMC E5 LV, HPMC E15, PVA, PVP K30, and polymers were used individually and in ratio. Both the solutions were mixed vigorously with the help of a magnetic stirrer for thirty minutes, this solution immediately probe sonicated for 15 to 30mis ensuring that the solution did not turn hot.

Characterization of Meclizine Hydrochloride Nanosuspension

Particle size analysis and Polydispersity Index

Particle size analysis and the mean polydispersity index of Meclizine hydrochloride nanosuspension were measured using "Microtrac Nanotrac A150". The mean particle size (PS) and polydispersity index (PDI) of prepared Meclizine hydrochloride nanosuspensions were analyzed and measured and formulations with optimum characteristics were selected for further study[4,8].

Differential Scanning Calorimetry (DSC)

The differential scanning calorimetry (DSC) was performed by using DSC60 (Shimadzu Corporation, Japan.) detector. Sample of drug and formulation were crimped hermetically in an aluminum pans which were subjected to analysis against the reference pan by heating under the nitrogen gas, the pans were subjected to constant rising heat flow of 5°C/min from 30°C to 300°C. Heat flow was measured for drug and lyophilized nanosuspension formulation as function of temperature [17].

Formulation of Nanosuspension loaded mouth dissolving films of meclizine Hydrochloride

In the preliminary studies quantities of polymers and plasticizers were required for the film, the formulation was determined, part of this amount of stabilizers and surfactant were utilized in the formulation of nanosuspension and the remaining amount of plasticizer, salivary stimulating agent and sweetener were dissolved in sufficient quantity of Millipore water separately. Meclizine Hydrochloride nanosuspension was kept for stirring on a magnetic stirrer to which Polymeric solution was added slowly and stirred for 3hrs to get a homogenous mixture. The resulting solution was set aside to remove air bubbles was casted on a petri plate lubricated with glycerin and was kept overnight in a hot air oven for drying at 45°C. The films were cut in 2×4 cm² size and the good quality sample films were further selected to perform its characterization [8,9].

Characterization of Mouth-Dissolving Films

The formulated nanosuspension-loaded mucoadhesive mouth-dissolving films of Meclizine Hydrochloride were evaluated for the following properties.

Weight and thickness uniformity Mouth dissolving film

Weight and thickness uniformity of the films was measured after precisely cutting the film in 2×4 Cm² size, films from three different sites were taken and weighed on digital balance and thickness was determined using a *Vernier caliper* of which average weight and thickness were measured along with the standard deviation [4,8].

Folding endurance of Mouth dissolving Film

The folding endurance of mouth dissolving film was measured manually by repeatedly folding the precisely cut film of 2×4 Cm² size at the same place till it breaks and several times films can be

folded without breaking it apart was taken as the value of folding endurance. Readings were taken in triplicates and average folding endurance along with standard deviation was determined [8].

Surface pH of Mouth dissolving film

The surface pH of the mouth dissolving film was determined to check if the pH of the formulation was within the acceptable range to avoid irritation in the oral mucosa. The film was placed on the petri dish and the surface of the film was made wet with one drop of pH 6.8 phosphate buffer and a reading was taken by bringing the glass electrode in close contact with the surface of the film. Three readings were taken and average along with standard deviation was reported [8].

Swelling index of Mouth dissolving film

To study the hydration properties and swelling index, precisely cut film was weighed and placed on top of pre-weighed wire mesh. The wire mesh along with the film was then kept in a glass petri dish containing distilled water and its weight was measured until a constant weight was observed. The difference between initial and final weight of the film was calculated and divided by the initial weight of the film to determine the swelling index [8,12].

Percentage elongation of Mouth dissolving film

Percentage elongation was measured to determine the amount of maximum strain which can be applied without breaking the film. The length of the film of 2×4cm² was noted down, and the film was held between two clamps wherein one clamp was fixed stress was applied on the other side. Change in initial and final length was noted down and the difference was calculated by dividing the final length of the film by initial length of the film, readings were taken in triplicate average percentage elongation was recorded along with the standard deviation [9].

Tensile strength

Tensile strength is a mechanical property that determines the ability of film to tolerate the pulling force applied. The film was held between the two clamps where one end was fixed and stress was applied on the other end. "It is calculated by dividing the applied load at rupture by cross-sectional area of the film in g/cm²"[19].

Percent moisture loss of Mouth dissolving film

A percent moisture loss test of mouth-dissolving film was conducted to determine the physical and structural stability and integrity of the films. A pre-weighed film of size 2×4 cm^2 was placed in a desiccator containing activated silica gel and fused anhydrous calcium chloride. After a period of three days, strips were removed from the desiccator and weighed again. Percent moisture loss was determined by subtracting initial weight by the final weight and its percentage was calculated [4].

In-vitro disintegration time

The In-vitro disintegration time was determined visually using disintegration test apparatus containing a beaker filled with 400ml of pH 6.8 phosphate buffer maintained at i37±2ºC, precisely cut films of size 2×4 cm^2 were placed in each tube and the time taken by the film to disintegrate was noted[14,16].

Drug Content

The drug content in each film was determined by using a UV spectrophotometer, precisely cut films of size 2×4 cm^2 were taken from three distinct spots and were dissolved individually in a beaker containing 25ml of Millipore water: methanol (60:40) using a magnetic stirrer and filtered using *Whatman* filter paper and was transferred to 25ml volumetric flask. After suitable serial dilutions absorbance was measured at 230nm and the drug content was estimated [19].

Ex-vivo Mucoadhesive strength

Ex-vivo mucoadhesive strength of mouth dissolving film was measured by using a modified balance method. The strength required to detach the film from the model membrane was considered as mucoadhesive strength. Sheep buccal mucosa was used as the model membrane and a phosphate buffer solution of pH 6.8 was used as the moistening fluid. Freshly excised buccal mucosa was obtained from the slaughterhouse and stored immediately in saline water after collection and was later transferred to pH 6.8 phosphate buffer. The finely cut buccal membrane was tied to a glass slide placed on the flat stage. Mouth dissolving film was placed on the lower side of the hanging glass slide to the left arm of the balance, balanced by previously keeping 10gm weight on each side. A drop of pH 6.8 buffer solution was added to the surface of mucosa to moisten it and 10gm weight on the right side was removed which lowered the left arm causing sticking of the film placed on a hanging glass slide on the surface of the buccal mucosa. Then weights were slowly added till the film detached from the mucosal surface. The weight required to detach the film was taken as mucoadhesive strength. Readings were taken in triplicates, and average mucoadhesive strength and standard deviation were determined [20].

In-vitro Drug release study

In-vitro drug release studies of nanosuspension loaded mucoadhesive mouth dissolving films of Meclizine Hydrochloride were performed with help of USP type I dissolution test apparatus with temperature maintained at 37±5°c, the stirrer rotation speed of 50 rpm containing 300ml of phosphate buffer of pH 6.8 as dissolution medium. Films were placed in a basket and the basket was immersed into the dissolution medium from which samples of 1ml each were withdrawn at time intervals of 0.30,1,2,4,8,10,12,15 min and replaced with dissolution medium to maintain sink conditions. Samples were further diluted up to 10ml and analyzed by UV-visible-spectrophotometer by measuring absorbance at 230 nm [4,19].

Ex-Vivo drug permeation study

Ex-vivo drug permeation studies of formulated mouth-

dissolving film were carried out by using a modified *Franz* diffusion cell. Freshly excised sheep buccal mucosa was taken as a model membrane. Assembly was placed on the magnetic stirrer; a small magnetic bead was placed in the receptor compartment for agitation and it was filled with pH 6.8 phosphate buffer solution. The formulation was placed over buccal mucosa and it was placed in between the receptor and donor compartment and was fixed with the help of clamps. The temperature was maintained at 3737±5°c. 1ml of pH 6.8 phosphate buffer solution was added to the donor compartment and aliquots of 1ml were withdrawn from the receptor compartment at the time interval of 2, 4, 8, 10, 12, 15, 20, 30, 40, and 60 min respectively. Sink conditions were maintained. Aliquots withdrawn were diluted to 10ml and analyzed at 230nm spectro-photometrically and the percentage of drug permeation were determined [13,19].

Stability Study

Stability studies of pharmaceutical products are done to ensure the quality, efficacy and safety of the dosage form. It helps to establish the shelf life to support the label claims. Stability studies also allow the evaluation of formulation under the influence of different atmospheric conditions such as humidity, temperature and light. It provides information regarding the shelf life of formulation and their preferred storage conditions hence it has become an integral part of formulation development.

Stability studies were performed on the optimized formulations stored at two different storage conditions using a stability chamber for a period of 30 days

Normal Conditions - 25°C ± 2°C/ 60% RH±5%

Accelerated condition - 40°C ± 2°C/ 75%±5% RH

Films were wrapped in butter paper followed by another wrapping of aluminum foil. Films were evaluated for pH stability, disintegration time, and drug content after storage of 30 days and values were compared for change [19].

RESULTS AND DISCUSSION

Screening of polymers for formulation of placebo mouth-dissolving films

Screening of polymers was done to select the film-forming polymers that can be used in the preparation of nanosuspension by ultra-sonication assisted solvent anti-solvent technique and mouth dissolving film using solvent casting method. Initially, placebo films were prepared by changing the concentration of polymers. Films formed with low polymer concentration were brittle, non-continuous and sticky in nature therefore different batches of the film with varying polymer concentrations were formulated and batches of films showing satisfactory results were chosen for further study.

Characterization of blank mouth dissolving films

Characterization of blank placebo films were conducted by determining the folding endurance and disintegration time of the mouth dissolving films. All the films showed satisfactory flexibility and disintegration property. Result of which is given in the table 2

Table 2: Folding endurance and disintegration time of placebo films

Formulation code	Folding endurance	Disintegration time (s)
F1	Poor	16
F2	Poor	24
F3	Average	41
F4	Good	52
F5	Average	29
F6	Good	45
F7	Excellent	56
F8	Excellent	98
F9	Good	31
F10	Good	46

- Poor film – film formed with brittle and non-continuous surface
- Average film – film with folding endurance below 200
- Good films – films with folding endurance from 300-400
- Excellent films- films with folding endurance more than 400

Preparation and characterization of Meclizine Hydrochloride Nanosuspension

Meclizine hydrochloride Nanosuspensions were prepared by using a bottom-up approach. A saturated drug solution made with solvent was added to the anti-solvent which creates a high degree of supersaturation this results in the formation of amorphous or crystalline solids. Meclizine Hydrochloride was dissolved in methanol which has a better allowable concentration according to the ICH guidelines hence it was selected as the solvent for preparing the drug solution. Various polymers were selected for the formulation of nanosuspension, individually and in combination. These were further subjected to the determination of particle size and PDI data which shown in Table No. 3. Depending on this data Batch no NS6 was considered for further study to optimize the effect of stabilizer ratio and probe sonication amplitude on particle size and PDI.

Characterization of Meclizine Hydrochloride Nanosuspension

Particle size analysis and Polydispersity Index

Particle size analysis and the mean polydispersity index of Meclizine hydrochloride nanosuspension were measured using "Microtrac Nanotrac A150" reading which are given in Table 4. The mean particle size (PS) and polydispersity index (PDI) of prepared meclizine hydrochloride nanosuspensions were analyzed and measured and results of the same are given in Figure 2 and 3. The value of PDI in all nanosuspension was below 0.8, indicating good homogeneity.

Table 3: Formulation of Meclizine HCL nanosuspension using different stabilizers

Batch no	Nanosuspension composition	Particle size (nm) Mean Volume	Polydispersity Index
NS1	3% HPMC E5 LV + Drug	789nm	0.390

NS2	4% HPMC E5 LV + Drug	912nm	0.471
NS3	5% HPMC E5 LV + Drug	3,900nm	3.09
NS4	3% HPMC E15 + Drug	1,273nm	1.889
NS5	3% HPMC E 15 + 1.5% PVP (2:1) + Drug	259.2nm	13.34
NS6	2% HPMC E15 + 1% PVP K 30 + Drug	426nm	0.142

Table 4: Particle size and polydispersity index of NS1, NS2, NS3, and NS4.

Batch	Drug in (mg)	Stabilizer ratio (SR)(%W/V)	Probe sonication amplitude (PSA)	Particle size (nm)	Polydispersity index
MCZ HCL NS1	25	0.5:2	45%	1,037nm	0.511
MCZ HCL NS2	25	0.5:2	65%	645.0nm	0.465
MCZ HCL NS3	25	1:2	45%	789.0nm	0.397
MCZ HCL NS4	25	1:2	65%	426.0nm	0.142

Figure 2: Particle Size and PDI of Meclizine HCL Nanosuspension (formulation2)

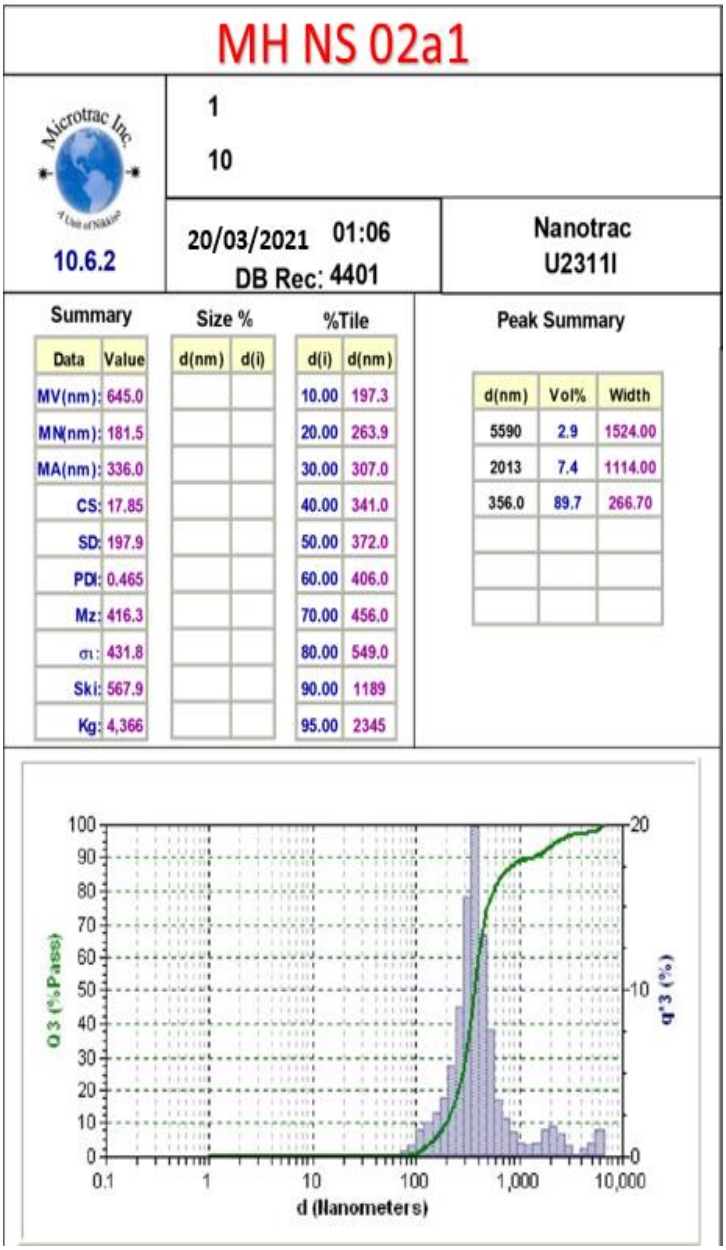
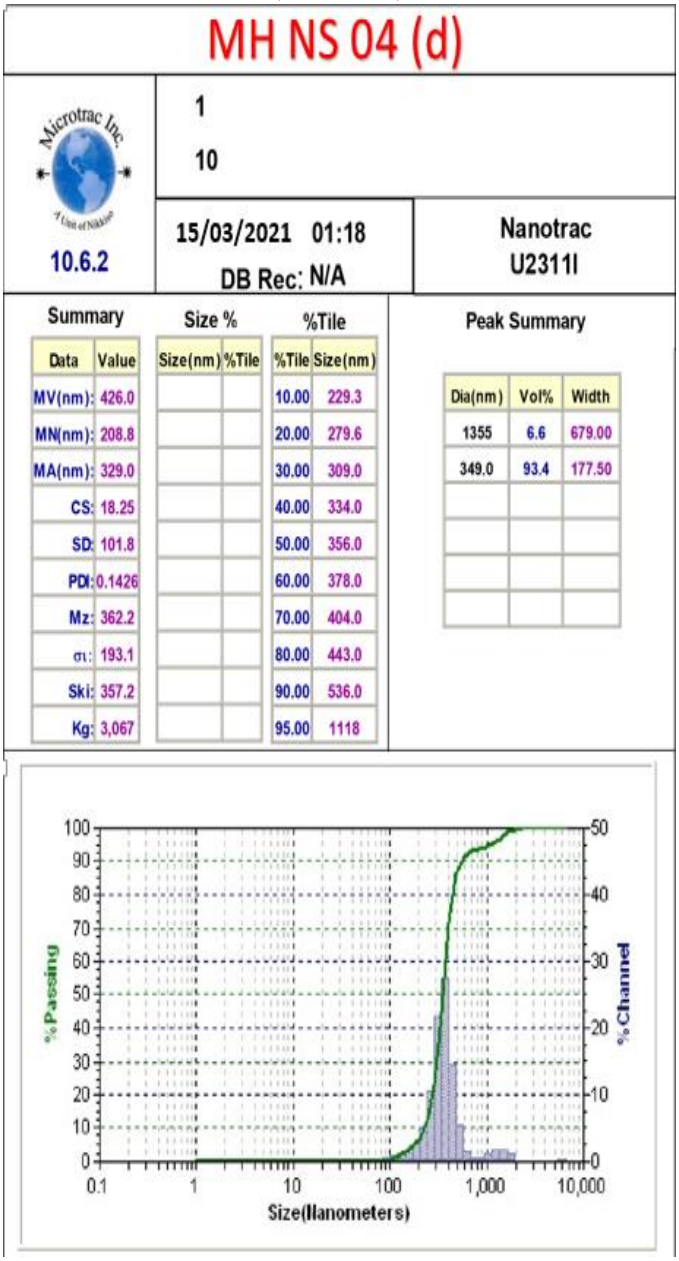


Figure 3: Particle size and PDI of Meclizine HCL Nanosuspension (formulation 4)



Differential Scanning Calorimetry (DSC)

The melting point of pure Meclizine HCL was found in the

range of 213-224°C DSC thermogram peak of pure drug Meclizine hydrochloride. DSC thermograms of Meclizine nanosuspension exhibited the disappearance of drug melting endothermic peak. This proves that drug nano-particles are embedded in a polymeric matrix suggesting that a change from the crystalline state to the amorphous state took place.

Figure 4: DSC thermogram of Meclizine HCL

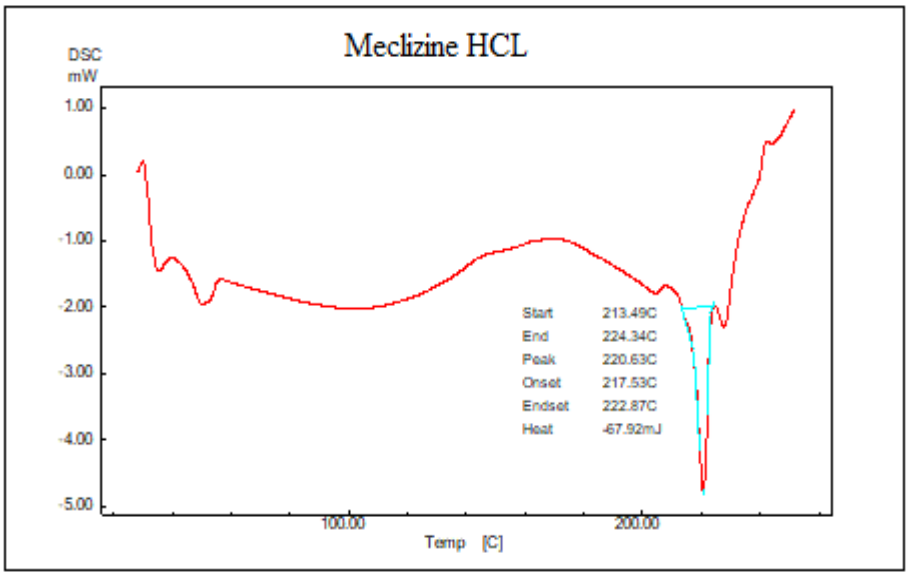
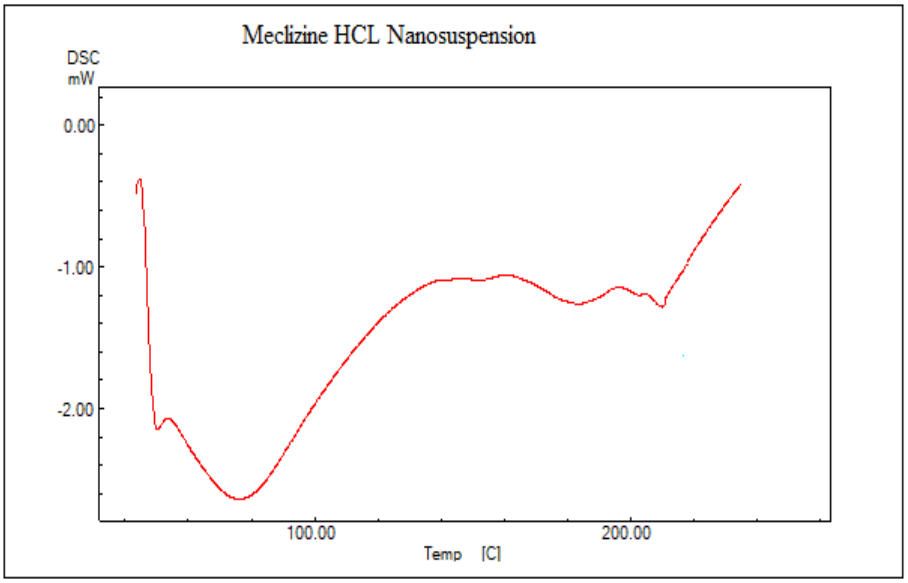


Figure 5: DSC thermogram of Meclizine HCL nanosuspension



Formulation of Nanosuspension loaded mouth dissolving films of meclizine Hydrochloride

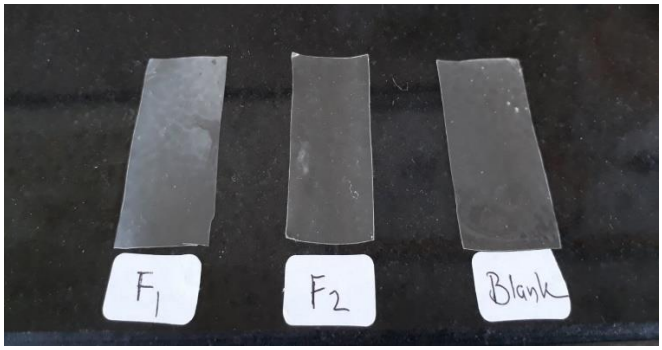
From the formulated Nanosuspensions, two formulations MCZ HCL NS02 and MCZ HCL NS04 were chosen to be incorporated into the mouth-dissolving films based on the results obtained from the optimization study (Table 5).

Nanosuspension-loaded mucoadhesive mouth-dissolving films of Meclizine Hydrochloride were successfully formulated by using the solvent casting method in which HPMC E15 and PVP K30 were used as film-forming polymers as shown in Figure 6. Propylene glycol was used as a plasticizer. Citric acid was used as a salivary stimulating agent and sodium saccharine was used as a sweetener. 5 perfect films free from bubbles and wrinkles were obtained in a batch which was further used for evaluating various parameters of the film.

Table 5: Formulation table of mouth dissolving films

Polymers	MDF1	MDFF2
Meclizine Hydrochloride	25mg	25mg
HPMC E 15 (%w/v)	2%	2%
PVP K 30 (%W/V)	0.5%	1%
Propylene Glycol (%v/v)	10%	10%
Citric acid (%w/v)	0.5%	0.5%
Sodium saccharine (%w/v)	0.25%	0.25%
Millipore water	q.s	q.s

Figure 6: Precisely cut meclizine hydrochloride nano-suspension loaded mucoadhesive mouth dissolving film formulations



Characterization of Mouth-Dissolving Films

Weight and thickness uniformity Mouth dissolving film

The result of weight and thickness uniformity of the formulations had no significant drastic change as there was not much difference between the amounts of film-forming polymers used in the formulation result of the same is given in Table 6.

Table 6: Result of weight and thickness uniformity of MDF

Formulation code	Weight (mg)*	Thickness uniformity (mm)*
MDF1	88±0.624	0.146±0.005
MDF2	93.7±0.458	0.163±0.011

*Data Expressed as Mean ± S.D. (n=3) MDF Mouth Dissolving Film

Folding endurance of Mouth dissolving Film

The folding endurance of mouth-dissolving film was found to increase slightly with an increase in the concentration of PVP K30 but the change was not very significant. The results of folding endurance are given in Table 7.

Table 7: Result of folding endurance of MDF

Formulation code	Folding endurance*
MDF1	458.33±0.577
MDF2	464.66±1.154

Surface pH of Mouth dissolving film

The surface pH of all the mouth-dissolving films of Meclizine HCL was found within the close range of neutral pH suggesting that there will be no significant irritation to the oral mucosa thus complying with the patient's acceptance. The result of the same is given in Table 8.

Table 8: Surface pH of MDF

Formulation code	Surface pH
MDF1	6.81±0.03
MDF2	6.8±0.01

Swelling index of Mouth dissolving film

Results of the swelling index indicated that the swelling index is higher in the formulation in which the PVP K30 is used in lesser amounts and the swelling index is less when the amount of PVP K30 used was more. Swelling index effects, the percentage of drug release. The result of the swelling index is given in Table 9.

Percentage elongation of Mouth dissolving film

Physical strength and flexibility are important factors that can be determined by evaluating the percentage elongation of the film. Formulation MDF2 showed a slightly higher percentage elongation, the result of which is given in Table 10.

Table 9: Swelling index of MDF

Formulation code	Swelling index
MDF1	0.202±0.001
MDF2	0.202±0.001

Table 10: Percentage elongation and Tensile strength of mouth-dissolving films

Formulation code	**Percentage elongation (%)**	**Tensile strength (g/cm²)**
MDF1	10.16±0.28%	30.3±0.25
MDF2	11.83±1.15%	36.75±0.31

Tensile strength

Tensile strength is a mechanical property that determines the ability of film to tolerate the pulling force applied. All the films had tensile strength in the acceptable range which means films had good mechanical strength, the result of which is shown in Table 8.

Percent moisture loss of Mouth dissolving film

A percent moisture loss test of the mouth-dissolving film was conducted to determine the physical and structural stability and integrity of the films. Moisture loss was slightly high in MDF1 as compared to MDF2, overall, it was not much significant which means formulated mouth-dissolving films had good physical and structural stability. The result is given in Table 11.

Table 11: Percentage moisture loss of mouth-dissolving films

Formulation code	**Percent moisture loss**
MDF1	4.88 ±0.01
MDF2	1.74 ± 0.01

In-vitro disintegration time

The In-vitro disintegration time was determined visually using disintegration test apparatus, all formulations showed satisfactory disintegration time. MDF2 showed better and faster disintegration which showed that disintegration time decreases with an increase in the concentration of PVP K30. Results of the same are given in Table 12

Table 12: *In-vitro* disintegration time of Mouth dissolving films

Formulation code	**Disintegration time (s)**
MDF1	46.28±0.560
MDF2	31.15±1.273

Drug Content

Drug content uniformity in each film was determined by using a UV spectrophotometer, to ensure uniform drug distribution. The results showed that there was uniformity in drug distribution in all formulation results as shown in Table 13.

Table 13: Drug content of mouth-dissolving films

Formulation code	**Drug content (%)**
MDF1	87.93 ±0.61%
MDF2	92.43±0.49%

Ex-vivo Mucoadhesive strength

Ex-vivo mucoadhesive strength of mouth dissolving film was measured by using a modified balance method. The strength required to detach the film from the model membrane was considered as mucoadhesive strength. Readings were taken in triplicates, and

average mucoadhesive strength and standard deviation were determined. It showed that the films made with a higher concentration of PVP K30 had better mucoadhesive strength as compared to films made with a lower concentration of PVP K30. The result of the same is given in Table 14.

Table 14: Mucoadhesive strength of mouth dissolving films

Formulation code	Mucoadhesive Strength (g/cm²)
MDF1	16.66±1.527
MDF2	31±1.732

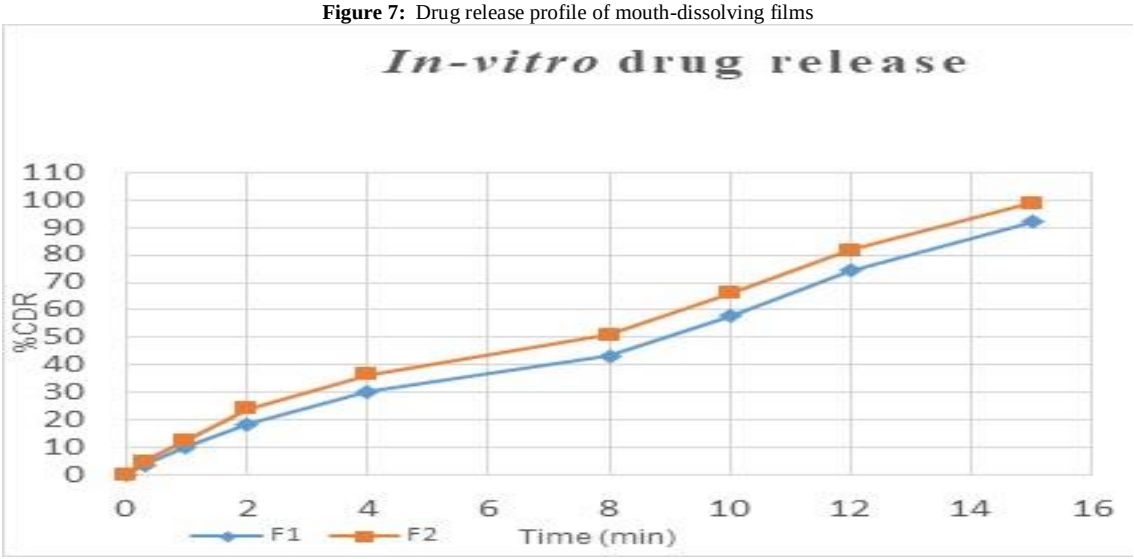
In-vitro Drug release study

In-vitro drug release profiles of the formulations suggested that there was a difference in drug release based on the composition of the film-forming polymers used. The rate of percentage drug release increased as the concentration of PVP K30 increased. PVP K30 works as a disintegrant and enhances the dissolution rate leading to faster drug release. Formulation MDF2 had maximum drug release at the end of the 15-minute study results which are shown in Table 15. Hence the formulation of MDF2 was considered for further studies. The drug release profile of formulations is shown in Figure 6.

Table 15: *In Vitro* drug release profile of mouth dissolving films

Time (min)	%CDR MDF1	%CDR MDF2
0	0%	0%
0.30	3.78%	4.92%
1	10.39%	12.71%
2	18.51%	24.24%
4	30.22%	36.61%
8	43.33%	50.87%
10	57.85%	66.05%
12	74.15%	81.71%
15	91.85%	98.72%

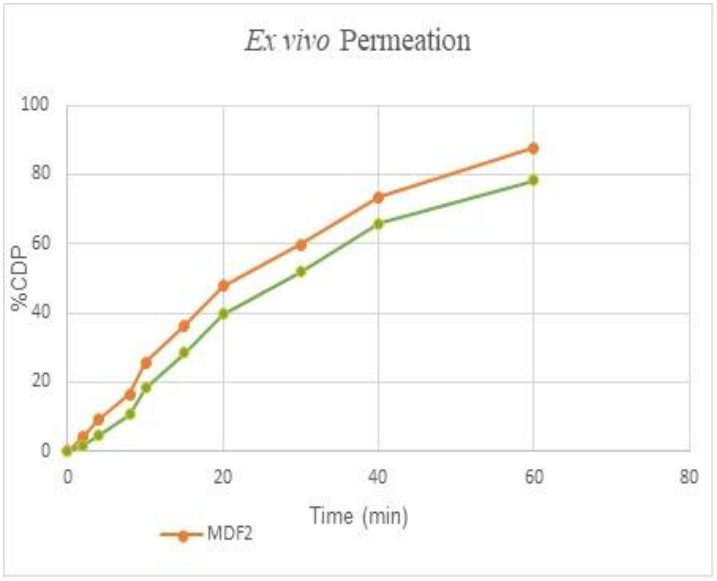
Figure 7: Drug release profile of mouth-dissolving films



% CDR Percentage cumulative drug release

Ex-Vivo drug permeation study

Ex-vivo drug permeation studies of optimized formulation loaded with nanosuspension MDF2 in comparison with the plain drug-loaded film were carried out by using a modified *Franz* diffusion cell as shown in Figure 8. The study was conducted to determine the rate of permeation of the drug through the model membrane. The study was conducted for 60min and samples of 1ml were withdrawn at different time intervals. The graph of the percentage of drug permeated against the time was plotted after calculations, the formulation MFD2 showed a higher percentage of permeability at a faster rate result of which are shown in Table 16 and depicted in Figure 5.



%CDP (Percentage cumulative drug permeation)

Figure 8: %CDP of Mouth dissolving film 2 and Plain drug-loaded film

Table 16: *Ex-vivo* drug release profile of mouth-dissolving films

Time (min)	% CDP MDF2	%CDP Plain drug
0	0%	0%

2	4.2%	1.8%
4	9.21%	4.6%
8	16.48%	10.65%
10	25.6%	18.24%
15	36.26%	28.49%
20	47.74%	39.54%
30	59.84%	51.86%
40	73.37%	65.75%
60	87.83%	78.33%

MDF Mouth Dissolving Film

Stability Study

The stability studies on formulation F2 was carried out as per ICH guidelines for a span of 30 days. The films were checked for changes in pH, disintegration time, and %drug content. The nanosuspension-loaded mouth-dissolving films of meclizine hydrochloride was found to be chemically and physically stable which showed no significant change in terms of physical properties such as disintegration time, pH, and percentage drug content. Formulation MDF2 showed no significant change in appearance after 30 days of storage where films were wrapped in butter paper followed by the aluminum foil in a self-sealable polythene bag. No significant changes were observed under the normal circumstances at room temperature however slight variations in the acceptable range were observed when the formulations were stored in accelerated conditions at 40°C ± 2°C 75% ±5% RH, hence formulation MDF2 had an acceptable stability profile as observed from the short-term stability studies conducted after 30 days, in room conditions (25°C ± 2°C 60% ±5% RH) as well as accelerated conditions (40°C ± 2°C 75% ±5% RH) as shown in table 17.

Table 17: Result of stability study of mouth dissolving films

Evaluation parameters	**Initial (Zero days)**	**Normal Conditions 25°C ± 2°C 60% ±5% RH 30 Days**	**Accelerated condition 40°C ± 2°C 75% ±5% RH 30 Days**
	MDF2	MDF2	MDF2
pH	6.8	6.82	6.78
Disintegration time (sec)	31±1.732	32.82±0.255	34.15±0.616
Drug content	92.96%	92.12%	88.73%

MDF Mouth Dissolving Film

CONCLUSION

A bottom-up process like the solvent/ antisolvent method is suitable and efficient for the formulation of Meclizine hydrochloride Nanosuspension using probe sonication. The solvent casting method is suitable for the formulation of nanosuspension-loaded mucoadhesive mouth-dissolving films. In-vitro drug release studies indicate that nanosuspension-loaded mucoadhesive mouth-dissolving film has a rapid drug release rate as compared to plain drug-loaded mouth-dissolving films and marketed tablet formulation.

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Conflict of interest

The authors have no conflicts of interest regarding this investigation.

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REFERENCES

1. Lakshmi P, Kumar G, 2010. Nanosuspension technology: A review. Int J Pharm Pharm Sci. Pages - 35-40. Doi: 10.52711 /2231-5713.2021.00042.

2. Jayalakshmy R, Sreethu KS, 2021. Nano-suspensions: a method for solubility enhancement. J. Med. P'ceutical Allied Sci, Pages - 2763-2771. Doi: 10.22270/jmpas.V10I 3.1070 https://jmpas.com/abstract/522

3. Gosavi DS, Akarte AM, Chaudhari PM, et.al, 2021. Mouth dissolving films: a review. World J. Pharmac. Res, Pages - 187-209.Doi:10.20959/wjpr20219-20973 wjpr.net/archive_show/2021/VOLUME%2010,%20JULY%20SPECIAL%20ISSUE%209

4. Elshafeey AH, El-Dahmy RM, 2021. Formulation and development of oral fast-dissolving films loaded with nanosuspension to augment paroxetine bioavailability: In vitro characterization, ex vivo permeation, and pharmacokinetic evaluation in healthy human volunteers. Pharmaceutics, Pages – 1869-1672. Doi: 10.3390/ pharmaceutics13111869

5. Bala R, Pawar P, Khanna S, et.al, 2013. Orally dissolving strips: A new approach to oral drug delivery system. Int J Pharma Investig, Pages - 67-76. Doi: 10.4103%2F2230-973X.114897

6. Vemula SK, Vangala M, 2014. Formulation development and characterization of meclizine hydrochloride sublimated fast-dissolving tablets. International scholarly research notices, Pages - 1-9.Doi: 10.1155/2014/281376

7. Malviya V, 2022 Design and Characterization of Thermosensitive Mucoadhesive Nasal Gel for Meclizine Hydrochloride. International Journal of Pharmaceutical Sciences and Nanotechnology, Pages - 5782-5793.Doi: 10.37285/ijpsn.2022.15.1.6

8. Rana P, Murthy RS, 2013. Formulation and evaluation of mucoadhesive buccal films impregnated with carvedilol nanosuspension: a potential approach for delivery of drugs having high first-pass metabolism. Drug delivery, Pages - 24-35. Doi: 10.3109/10717544.2013.779331

9. Chonkar AD, Rao JV, Managuli RS, et.al, 2016. Development of fast dissolving oral films containing lercanidipine HCl nanoparticles in semicrystalline polymeric matrix for enhanced dissolution and ex vivo permeation.

European journal of Pharmaceutics and Biopharmaceutics, 179-91. Doi: 10.1016/j.ejpb.2016.04.001

10. Chavan DU, Marques SM, Bhide PJ, et.al, 2020. Rapidly dissolving Felodipine nanoparticle strips-Formulation using Design of Experiment and Characterisation. Journal of Drug Delivery Science and Technology, 102053. Doi: 10.1016/j.jddst.2020.102053

11. Pavankumar G V, Ramakrishna, V, William GJ, et al, 2005. Formulation and evaluation of buccal films of salbutamol sulphate. Indian journal of pharmaceutical sciences, Pages 160 – 162.

12. Linku Abraham,Joseph Sijimol, 2018. Formulation and Evaluation of Fast Dissolving Oral Film of Anti-Allergic Drug, Asian Journal of Pharmaceutical research and Development. Pages - 5-16 Doi: 10.22270/ajprd.v6i3.374

13. Saab M, Mehanna M M 2019. Disintegration time of orally dissolving films: various methodologies and in-vitro/in-vivo correlation. Die Pharmazie-An International Journal of Pharmaceutical Sciences, Pages - 227-230. Doi: 10.1691/ph.2019.8231

14. Dharmasthala S, Shabaraya AR, Andrade GS, et al, 2019. Fast Dissolving Oral Film of Piroxicam: Solubility Enhancement by forming an Inclusion Complex with β-cyclodextrin, Formulation and Evaluation. J Young Pharm. Pages 1-6. Doi: 10.5530/jyp.2019.11.1 jyoungpharm.org/25 0 7 /

15. Imtiaz N, S B Majee, G R Biswas, 2021. Development and characterization of oral swellable rapid release film with superdisintegrant-surfactant. International Journal of Current Pharmaceutical Research, Pages - 75-80. Doi: 10.22159/ijcpr.2021v13i1.40821.journals.innovareacad emics.in/index.php/ijcpr/article/view/40821

16. Hao J, Gao Y, Zhao J, et al 2015. Preparation and optimization of resveratrol nanosuspensions by antisolvent precipitation using Box-Behnken design. AAPS PharmSciTech. Pages - 2118-2128. Doi: 10.1208/s12249-014-0211-y

17. Vemula SK, Vangala M, 2014. Formulation Development and Characterization of Meclizine Hydrochloride Sublimated Fast Dissolving Tablets. Int Sch Res Notices. 281376. Doi: 10.1155/2014/281376 hindawi.com/journals /isrn/2014/281376/

18. Saili PM, Dandagi PM, Yashaswini L et al 2017. Development and Characterization of Fast Dissolving Oral Films of Orciprenaline Sulphate. Indian J of Pharmaceutical Education and Research. Pages- 536 -542 . Doi: 10.5530/ ijper.51.4.82jper.org/sites/default/files/10.5530ijper .51.4.82.pdf

19. Palem, CR, Gannu, R, Doodipala, N, et al, 2011.Transmucosal delivery of domperidone from bilayered buccal patches: In Vitro, Ex Vivo and In Vivo characterization. Arch. Pharm. Res. Pages - 1701–1710. Doi: 10.1007/s12272-011-1014-2

20. SM, V.K., Roy, A.K., 2011. Formulation and evaluation of mucoadhesive buccal tablets for antihypertensive drug Valsartan (Doctoral dissertation, Acharya & BM Reddy College of Pharmacy (ABMRCP)). 13.232.72.61:8080/ jspui/handle/123456789/6572