

RESEARCH ARTICLE

In-vitro and *In-vivo* Evaluation of Cevimeline HCl Fast Dissolving Films

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Received: 18th September, 2023; Revised: 22th October, 2023; Accepted: 25th November, 2023; Available Online: 25th December, 2023

ABSTRACT

The primary aim and objective of the present work was to formulate the cevimeline HCl fast-dissolving films and assess the films, a pharmaceutical compound utilized for the management of xerostomia symptoms linked to Sjogren's disease. Fast-dissolving films of cevimeline HCl were formulated by utilizing the solvent casting technique and the sodium carboxy methyl cellulose, HPMC E5, polyvinyl alcohol, and polyvinyl pyrrolidone were used as film-forming agents. Additionally, polyethylene glycol 600 and sodium starch glycolate were used as a super disintegrant and plasticizers. The formulation contains citric acid and stevia powder, which serve the purpose of stimulating saliva and providing sweetness, respectively. This study focused mainly on the development and assessment of cevimeline HCl fast-dissolving films, specifically examining parameters such as film thickness, folding resistance, drug content, air bubble entrapment, and film curling. The obtained results were found to be consistent with the preset ranges established for these parameters. The drug release from the fast-dissolving films formulated with PVP K30 was 99.91% released within 5 minutes timeframe. The results indicates that the films prepared with PVP K30 show enhanced solubility, rate of dissolution, flexibility, and tensile strength in comparison to the films formulated with sodium carboxy methyl cellulose, HPMC E5 and Polyvinyl alcohol. Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) studies were done to characterize the pure drug, polymers and to C11 the optimized formulation. These findings indicated, no observed incompatibilities among the drug and polymers utilized in this study. Moreover, *in-vivo* investigations were conducted on optimized formulation C11, which demonstrated its notable stability.

Keywords: Cevimeline HCl, Solvent casting, Sodium carboxy methyl cellulose, HPMC E5, Polyvinyl alcohol, PVP K30, Plasticizers, Superdisintegrants.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.4.16

How to cite this article: Akash V, Shailaja P. *In-vitro* and *In-vivo* Evaluation of Cevimeline HCl Fast Dissolving Films. International Journal of Drug Delivery Technology. 2023;13(4):1213-1221.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

There is a growing interest within the pharmaceutical industry in the development of expedited drug delivery systems. These systems frequently undergo dissolution or disintegration within a little time frame, without necessitating mastication or the presence of water. Recently, there has been a proposal for the use of orodispersible films, which are developed to dissolve and disintegrate rapidly within the buccal cavity. The issue of patients experiencing choking incidents has significantly diminished with the introduction of fast-dissolving tablets as a viable alternative.^{1,2} Orodispersible formulations offer distinct benefits for both the geriatric population and youngsters, as they allow for the avoidance of the need to ingest substantial quantities of fluids during administration.³ The aforementioned dosage forms possess numerous advantages in comparison to liquid dosage forms.⁴ These advantages encompass precise dosing, elimination of water requirement, and absence of choking hazards, which distinguishes them from tablets and capsules.⁵ Furthermore, it should be noted that despite the rapid

dissolution of oral disintegrating tablets, the residual fragments they generate remain insoluble until they are ingested.^{6,7} The fast-dissolving dosage forms are commonly called by many researchers using a wide range of terms, such as orodispersible film, mouth dissolve, quick dissolve, orally dissolve, mouth dissolve, or melt-in-mouth dosage forms.⁸ These patches possess an active substance or medicinal excipients and exhibit a thickness comparable to that of postage stamps.⁹ The sublingual mucosa's thin membrane and high perfusion contribute to the rapid absorption of medication and its fast bioavailability. This is facilitated by the relative permeability of the sublingual mucosa and the quick commencement of drug activity.

The Discharge Mechanism¹⁰

The administration of the delivery system involves placing it directly onto the patient's tongue or another mucosal tissue within the oral cavity. The presence of water-soluble polymer and other excipients facilitates the rapid moistening of the film by saliva, leading to swift hydration and adhesion

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to the application site. Subsequently, the film dissolves, enabling the release of the medicine for absorption through the oromucosal route. The substance rapidly undergoes dissolution or disintegration, facilitating the release of the drug for absorption through the mucosal membrane. Alternatively, with appropriate modifications, it allows for absorption through the gastrointestinal tract by oral administration, exhibiting fast-dissolving properties. Cevimeline hydrochloride is a pharmacological agent that exhibits cholinergic properties by stimulating the salivary and sweat glands which are exocrine in nature. This drug specifically has a higher binding affinity towards M3 muscarinic receptors. The usage of this treatment is meant to treat the xerostomia symptoms commonly seen in individuals diagnosed with Sjogren's syndrome.¹¹ The administration of cevimeline hydrochloride involves oral ingestion of a 30 mg capsule, with a recommended frequency of three times per day.¹² The quick absorption of the substance is evidenced by its time to reach maximum concentration, which occurs within 1.5 to 2 hours following the administration of a single dosage. Following the administration of many doses, there was no observed accumulation of either the active pharmaceutical ingredient or its metabolites.¹³⁻¹⁵

MATERIALS AND METHODS

Cevimeline HCl a gift sample from Alkem Laboratories Bangalore, sodium carboxy methyl cellulose, HPMC E5, polyvinyl alcohol, and polyvinyl pyrrolidone were obtained from Yarrow chem, Ltd., Mumbai, Stevia powder which is natural disintegrant obtained from High-pure fine Chem., Chennai.

Preparation of Cevimeline HCl fast-Dissolving Films

The fast-dissolving films of cevimeline HCl were fabricated by using the solvent casting method. In order to achieve solutions with transparency, various film-forming polymers, including sodium carboxy methyl cellulose, HPMCE5, polyvinyl alcohol, and polyvinyl pyrrolidone were separately dissolved in aqueous solutions within 100 mL beakers. The prescribed quantities of cevimeline HCl, sodium starch glycolate, stevia powder, citric acid, and PEG 400 were weighed and dissolved in the aforementioned aqueous media. The resulting mixture was well blended to achieve a homogenous mixture. The resultant mixture was applied onto a non-adhesive substrate and subjected to a 24-hour curing process under an infrared lamp. After the films had undergone thorough drying, they were subsequently trimmed to achieve the necessary sizes.^{16,17} Numerous endeavors were undertaken to enhance the formulation of rapid-dissolving films containing cevimeline HCl. The composition of cevimeline HCl fast-dissolving films were given in Table 1.

The resultant solution was applied onto a non-adhesive substrate and subjected to a 24-hour drying period under an infrared lamp. After the films had completed the drying process, they were cut into the appropriate dimensions. Several experiments were conducted to enhance the preparation process of cevimeline HCl fast-dissolving films. The following

is list of the ingredients in cevimeline HCl fast-dissolving films were given in Table 1.

Physical Evaluation of Cevimeline HCl fast Dissolving Films¹⁸

The physical properties of the cevimeline HCl fast-dissolving films were assessed, including thickness uniformity, folding endurance, and drug content homogeneity. Results of the physical evaluation were given in Table 2.

Thickness uniformity

The formulated films were evaluated for film thickness at several locations with the help of screw gauge with a measurement of a minimum increment 0.01 mm. In the context of film, the thickness was measured at three specific locations and subsequently, the average value was computed. The outcomes are noted in Table 2.

Folding endurance

The flexibility measurement of the film's is sometimes referred to as folding endurance. The film's resistance to folding was assessed through the iterative process of folding a narrow strip of the material until it reached its breaking point. A film's folding endurance can be determined by how many folds a film can withstand before breaking. The outcomes are presented in Table 2.

Drug content uniformity

UV-visible spectrophotometric analysis was conducted on the films in order to assess the consistency of their drug content. The films obtained from the casting process were subjected to three consecutive slicing operations to achieve the desired sizes. The cut film samples were individually placed into volumetric flasks of 100 mL and subsequently dissolved in media of pH 6.8 phosphate buffer solution. Then 1-mL of solution was taken from each flask and transferred in to 10 mL volumetric flask with the help of a pipette and the total volume was adjusted by using phosphate buffer of 6.8 pH. The resultant solution absorbance was determined at a λ_{max} of 207 nm using a UV-visible spectrophotometer, with a blank serving as the reference. By using a typical graph the percentage uniformity in drug content was measured.¹⁸ The observations collected are presented in Table 2.

The task of replicating natural conditions and accurately measuring oral films poses a significant challenge due to the complexities associated with determining disintegration and dissolution. This difficulty arises from the concurrent dissolution of oral films in a small volume of saliva. The medium employed in prior dissolution and disintegration studies was of considerable volume and lacked physiological representation within the mouth cavity. Various independent methodologies were employed to evaluate the disintegration and dissolution characteristics. This technique requires a minimal quantity of media.

Dissolution test by franz diffusion cell

The approximate volume of the Franz diffusion cell is 15 mL. A strip, measuring 10 mg in weight, is introduced

Table 1: Composition of cevimeline HCl fast dissolving films

Ingredients (w/w)	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Cevimeline HCl	30	30	30	30	30	30	30	30	30	30	30	30
Maltodextrin	40	40	40	40	40	40	40	40	40	40	40	40
Na CMC	80	90	100	-	-	-	-	-	-	-	-	-
HPMC E5	-	-	-	80	90	100	-	-	-	-	-	-
Polyvinyl alcohol	-	-	-	-	-	-	80	90	100	-	-	-
Polyvinyl pyrrolidone K30	-	-	-	-	-	-	-	-	-	80	90	100
PEG 600	10	10	10	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	5	5	5	5	5	5	5	5	5	5	5	5
Stevia Powder	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Citric acid	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Water (mL)	5	5	5	5	5	5	5	5	5	5	5	5

Table 2: Evaluation of physical parameters for cevimeline HCl fast dissolving films

Formulation	Weight uniformity (mg)	Drug content (mg/film)	Film thickness (mm)	Folding endurance (no)	Dispersion test	Curling
C1	159	28.22	0.032	98	Passed	Absent
C2	167	29.11	0.031	99	Passed	Absent
C3	178	28.77	0.033	97	Passed	Absent
C4	158	28.36	0.031	99	Passed	Absent
C5	169	29.91	0.032	97	Passed	Absent
C6	179	28.45	0.034	98	Passed	Absent
C7	159	29.88	0.031	99	Passed	Absent
C8	169	28.33	0.032	97	Passed	Absent
C9	180	29.14	0.034	98	Passed	Absent
C10	160	28.74	0.032	99	Passed	Absent
C11	169	29.63	0.033	104	Passed	Absent
C12	181	30.12	0.031	98	Passed	Absent

into the Franz diffusion cell, and along with it add 10 mL of 6.8 pH phosphate buffer which mimics the pH of saliva. The cell should be positioned on a magnetic stirrer, the bead inside the cell rotates at an rpm of 50 and the temperature was maintained at 32°C. Subsequently, extract 1-mL of samples at regular intervals of 1, 2.5, 5, 10 and 15 minutes. The extracted samples were diluted to 5 mL using pH 6.8 phosphate buffer and proceeded to measure the absorbance at 207 nm by using UV spectroscopy. A phosphate buffer of pH 6.8 was used as a blank for calibration purposes. The drug release plots of all the film formulations are seen in Figure 1.¹⁸

Dispersion test

Dispersion test of films, involves combining 200 mL of 6.8 pH buffer with a film strip containing 20 mg of cevimeline HCl, stirring the mixture for three minutes with a glass rod, and then passing the resulting solution through a 22-mesh screen.

In-vitro diffusion studies

In-vitro diffusion studies for all the fast-dissolving films were conducted by utilizing Franz diffusion cell in the phosphate buffer of pH 6.8. The studies on dissolution were conducted over the course of 15 minutes for each formulation. Dissolution tests were performed in triplicate under constant sink circumstances. A 5 mL aliquot of samples was obtained at predetermined intervals, which were filtered and analyzed spectrophotometrically at 207 nm. Release of the drug from all the formulated cevimeline HCl films were depicted in Figure 1.¹⁹

Evaluation of Various In-vitro Dissolution Parameters

The parameters such as T_{50} , T_{90} , DE5% were determined from dissolution data and the rate constant for first-order release of all the formulations were determined from the dissolution data and the findings were noted in Table 3.

Characterization

Diffusion studies provided the basis for optimizing and characterizing some of the formulations.

IR spectral studies²⁰

FT Bruker IR spectral analysis was performed on a selection of films. The studies were done in order to determine, the variations in structures of drug and excipient used in film before being subjected to dissolution experiments. The graphs of fourier transform infrared (FTIR) for pure drug, polymer and C11 the optimized formulation were seen in Figures 2-7, and the interpretation data was given in Table 4, respectively.

Differential scanning calorimetry²⁰

Diffusion imaging drug, polymers, and the final, improved formulation were all measured by calorimetry with the help of a SHIMZDO and DSC-60 differential scanning calorimeter. The samples were heated at a rate of 20°C/min which were maintained at a temperature range of 25 to 250°C in a hermetically sealed aluminum crucible. The thermograms of

various films were shown in Figures 8-13 and the DSC results are shown in Table 5.

Scanning electron microscopy

Using a sputter coater unit (SPI, Sputter, USA), a thin layer of gold was deposited to the samples. Then, a 10 kV scanning electron microscope (JSM-6390, Japan) was utilized to finally examine the sample. SEM photographs of pure drug and optimized formulation C11 was observed in Figures 14, 15 and the results were given in Table 5.

In-vivo pharmacokinetic studies of cevimeline HCL fast dissolving films

Rabbits were used for *in-vivo* pharmacokinetic studies of cevimeline HCl oral solution and cevimeline HCl optimized formulation C11. The plasma concentration of cevimeline HCl was measured using the UPLC method the formulations were administered through oral route to rabbits at a dose of 10 mg/kg body weight. The maximum concentration of drug in plasma (C_{max}), duration to peak plasma concentration

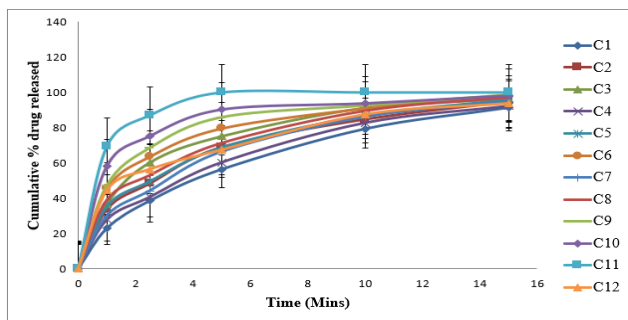


Figure 1: Drug release profiles for cevimeline HCl fast dissolving films

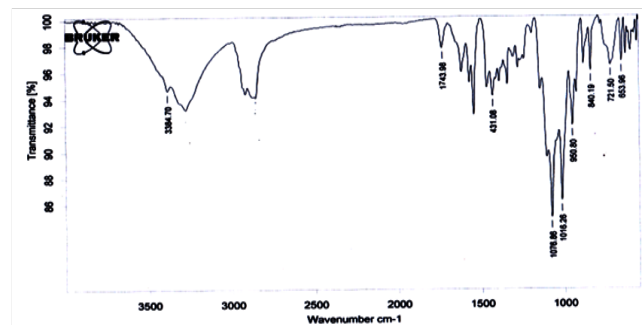


Figure 4: FTIR spectrum of sodium HPMC E5

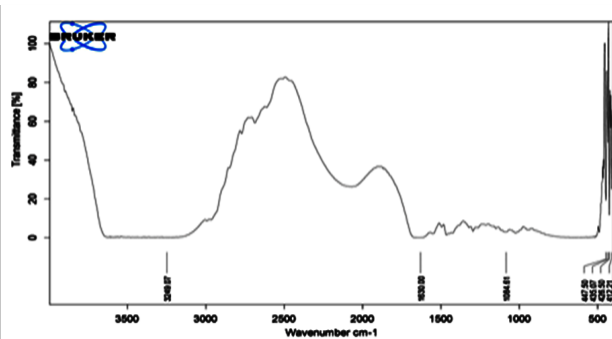


Figure 2: FTIR Spectrum of cevimeline HCl pure drug

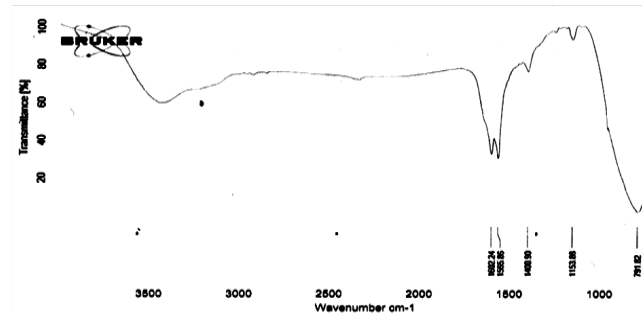


Figure 5: FTIR spectrum of sodium polyvinyl alcohol

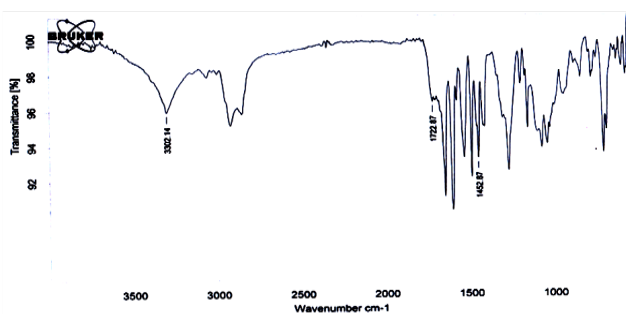


Figure 3: FTIR spectrum of sodium carboxy methyl cellulose

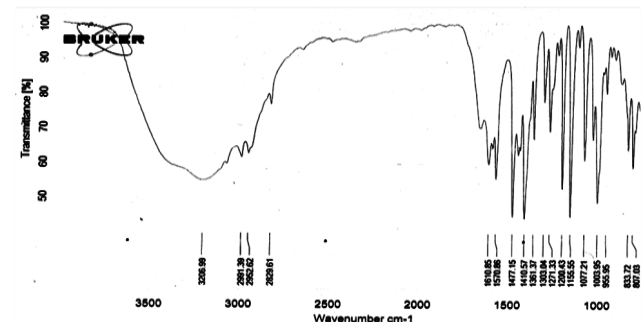


Figure 6: FTIR spectrum of sodium polyvinyl pyrrolidone

Table 3: Evaluation of *in-vitro* dissolution parameters for cevimeline HCl fast dissolving films

Formulation	T_{50} (min)	T_{90} (min)	DE %	First order K (min^{-1})	R^2
C1	4.7	14.7	18.44	0.152	0.955
C2	4.5	14.2	19.63	0.177	0.944
C3	4.0	14.0	22.51	0.145	0.932
C4	4.6	14.5	18.22	0.214	0.974
C5	4.2	14.0	19.23	0.236	0.944
C6	3.7	13.7	21.03	0.222	0.955
C7	4.4	14.4	19.22	0.233	0.966
C8	3.8	13.7	18.71	0.247	0.974
C9	3.4	9.4	21.25	0.221	0.958
C10	1.7	8.4	19.58	0.147	0.952
C11	1.3	4.4	22.36	0.187	0.987
C12	2.4	13.4	19.36	0.155	0.966

(T_{max}), biological half-life of the drug ($t_{1/2}$), area under plasma concentration versus time plot (AUC), and mean residence time (MRT) were all determined with the help of PK summit solutions software USA.^{21,22} The results were given in Table 6 and depicted in Figure 16.

RESULTS AND DISCUSSION

Preparation of Cevimeline HCl Fast Dissolving Films

The cevimeline HCl fast-dissolving films were prepared by using a solvent casting process utilizing a variety of film-forming ingredients, sodium carboxy methyl cellulose, HPMC E5, polyvinyl alcohol, polyvinyl pyrrolidone. A total 12 formulations were formulated, among all the formulations formulation C11 was prepared with PVP K30 and released the 99.91% drug within 5 minutes. This indicates that the films exhibit the release of drug at a faster rate and good folding endurance. The composition of cevimeline HCl fast-dissolving films was given in Table 1.

Evaluation of Physical Parameters for Cevimeline HCl Fast Dissolving Films

The films of cevimeline HCl were evaluated for physical parameters like weight variation, drug content uniformity, thickness of the film and folding endurance. The weight uniformity of all the films of cevimeline HCl prepared with Sodium carboxy methyl cellulose, HPMC E5, polyvinyl alcohol, polyvinyl pyrrolidone was maintained in the range of 158 to 181 mg. The content uniformity of dug in all the films of cevimeline HCl was maintained within the range of 28.22 to 30.12 mg, it indicates that the drug is evenly distributed in all the cevimeline HCl fast-dissolving film formulations. The film thickness of all cevimeline HCl fast-dissolving films was within the range of 0.030 ± 0.034 mm. The cevimeline HCl fast dissolving film folding endurance values were maintained in the range of 99 to 104 foldings. All the film formulations

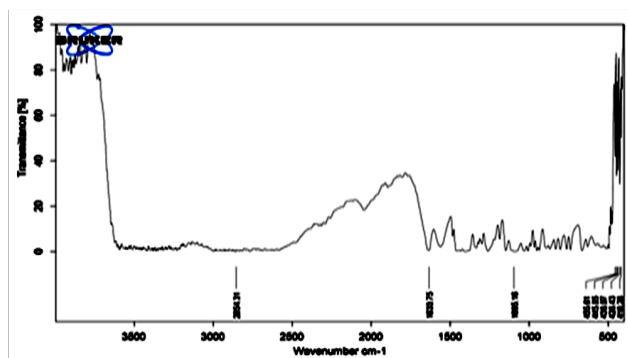


Figure 7: FTIR spectrum of optimized formulation C11

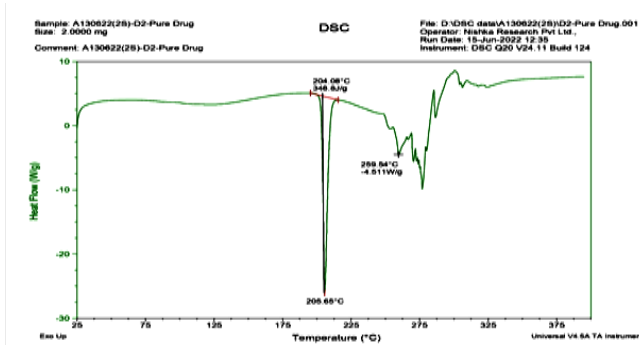


Figure 8: DSC thermogram of pure drug cevimeline HCl

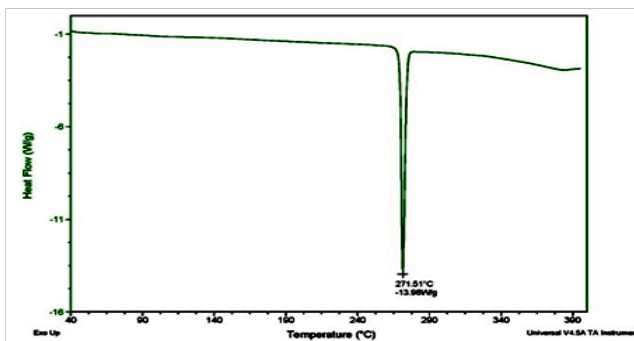


Figure 9: DSC thermogram of sodium carboxy methyl cellulose

were found to be stable and should have good tensile strength, therefore this suggests that they are. All the prepared films passed the dispersion test. Results for characteristics such as weight variation, drug content uniformity, thickness of the films, and folding durability were assessed; they are shown in Table 2.

In-vitro Diffusion Studies of Cevimeline HCl Fast Dissolving Films

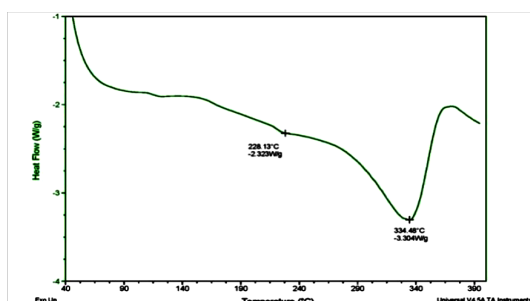
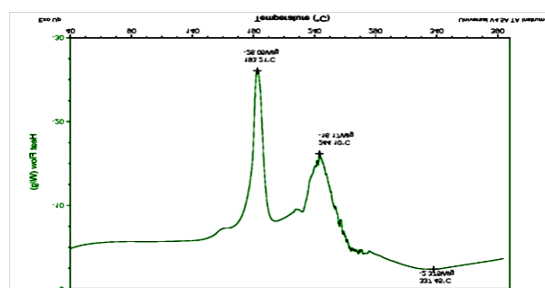
Diffusion studies were conducted for the cevimeline HCl fast-dissolving film formulations with the help of using Franz diffusion cell by using 6.8 pH phosphate buffer as dissolution medium. The film formulations C1-C3 of cevimeline HCl which were prepared by using sodium carboxy methyl cellulose exhibited an average drug release of 91.36 to 96.36% within 15 minutes. The formulations C4-C6 formulated by using HPMC E5, release the drug at an average of 92.26 to 98.36%

Table 4: Interpretation of FTIR spectrum

Functional group	Wave number (CM^{-1})					
	Pure drug	Na CMC	HPMC E5	PVA	PVP	C11
O-H Stretching	3640.14	-	3025.69	-	-	3452.39
C-H Stretching	3155.69	3001.58	3158.23	3337.25	3422.01	3381.02
C=O Stretching	1700.23	2125.36	2499.33	2036.11	2722.01	2227.33
C-H Bending	-	1478.22	1536.11	1755.12	1812.52	1788.66
C-O Stretching	1252.78	-	-	-	-	-
C-F Stretching, aromatic	-	836.33	901.26	922.36	888.36	922.87

Table 5: DSC thermogram interpretations

Cevimeline HCl	NaCMC	HPMC E5	PVA	PVP K30	Optimized formulation (C11)
205.65°C	271.33°C	220.13°C	183.31°C	103.66°C	133.36°C
Sharp endothermic Peak	Sharp endothermic Peak	Broad endothermic peak	Sharp endothermic peak	Broad endothermic peak	Broad endothermic

**Figure 10:** DSC thermogram of HPMC E5**Figure 11:** DSC thermogram of polyvinyl alcohol

within 15 minutes. The fast-dissolving film formulations C7-C9 prepared by using polyvinyl alcohol released the drug at an average of 94.58 to 98.44% within 15 minutes. The film formulations C10 and C12 which were prepared by using polyvinyl pyrrolidone exhibited an average drug release of 98.22 to 99.91% within 15 minutes. In comparison to all the films formulated, the optimized formulation C11 that was prepared by using PVP K30 showed improved drug release up to 99.91% within 5 minutes. The drug release profiles are shown in Figure 1.

Evaluation of Various *In-vitro* Dissolution Parameters

The parameters that were obtained from dissolution data, such as T50, T90, DE5% and the drug release rate constant for the first order were computed, and the observations were noted in Table 3. The optimized formulation C11 showed T50, T90, and DE 5% values of 1.3, 4.4, and 22.36%, respectively. All of the film formulations' first-order plots were linear. The release of the drug from all the formulations was linear and exhibits linear order release, with R2 values ranging 0.932 to 0.987. It shows that the drug release from the formulations is concentration-dependent and linear with the first-order release rate constant (K1).

Characterization Studies

Fourier-transform infrared spectroscopic analysis

Fourier transform infrared (FTIR) spectra of cevimeline HCl principle peaks were exhibited at wave numbers of 3640 cm^{-1} (O-H), 1700 cm^{-1} (C=O), and 1252 cm^{-1} (C-O). Sodium carboxy methyl cellulose exhibited principle peaks in FTIR studies at wave numbers of 3001.58 cm^{-1} (C-H Stretching), 2125.36 cm^{-1} (C=O Stretching), 1478.22 cm^{-1} (C-H bending), 836.33 cm^{-1} (C-F Stretching, Aromatic). The FTIR spectra of HPMC E5 show principle peaks at wave numbers of 3158.23 cm^{-1} (C-H Stretching), 2499.33 cm^{-1} (C=O Stretching), 1536.11 cm^{-1} (C-H bending), 901.26 cm^{-1} (C-F Stretching, Aromatic). The FTIR spectra of polyvinyl alcohol, principle peaks were observed at wave numbers of 3337.25 cm^{-1} (C-H Stretching), 2036.11 cm^{-1} (C=O Stretching), 1755.12 cm^{-1} (C-H bending), 922.36 cm^{-1} (C-F Stretching, Aromatic). The FTIR spectra of polyvinyl pyrrolidone showed principle peaks at wave numbers of 3381.02 cm^{-1} (C-H Stretching), 2827.33 cm^{-1} (C=O Stretching), 1788.66 cm^{-1} (C-H bending), 922.87 cm^{-1} (C-F Stretching, Aromatic). The optimized formulation E11 spectra exhibited all the principle peaks present in the cevimeline HCl pure drug. Thus there was

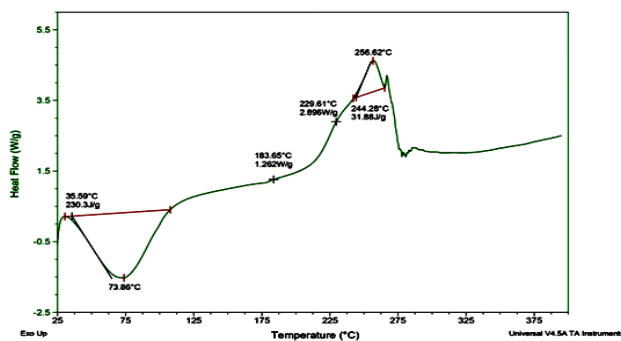


Figure 12: DSC thermogram of polyvinyl pyrrolidone

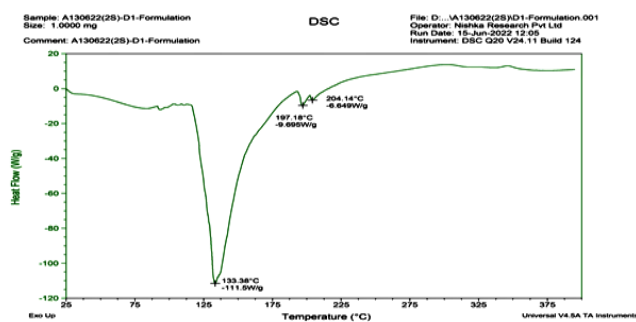


Figure 13: DSC thermogram of optimized formulation C11

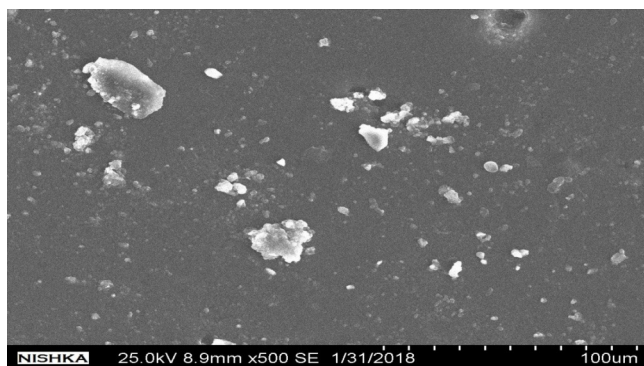


Figure 14: SEM photograph of cevimeline HCl pure drug

no characteristic peak appeared or vanished, proving that there was no chemical interaction between the drug and the polymer used in the formulation. The FTIR graph of pure drug, polymers and optimized formulation C11 were shown in Figures 2 to 7 and the interpretation values were given in Table 4.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) thermogram for cevimeline HCl was seen at temperature 205.65°C as sharp endothermic peak. The DSC thermogram exhibits a sharp endothermic peak for sodium carboxy methyl cellulose at 271.33°C as a sharp endothermic peak. The DSC thermographic peak for HPMC E5 showed a broad endothermic peak at 220.13°C. The peak of DSC for polyvinyl alcohol was seen at 183.31°C as sharp endothermic peak. A broad endothermic peak was observed for polyvinyl pyrrolidone in DSC thermogram at 103.66°C. The DSC thermographic peak

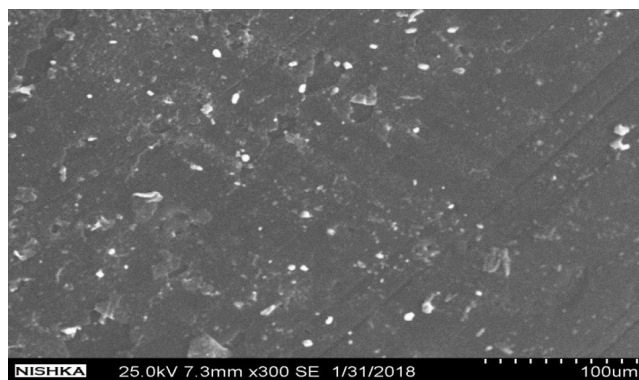


Figure 15: SEM photograph of optimized formulation (C11)

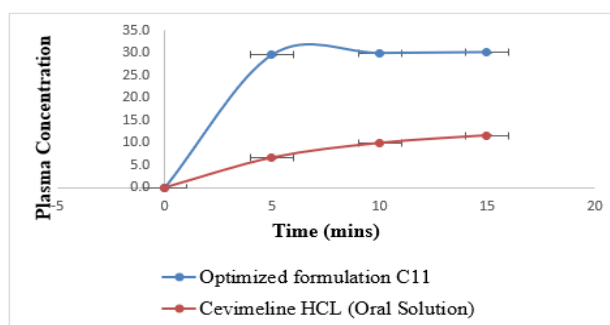


Figure 16: Drug release profile for optimized formulation (C11)

for optimized formulation C11 showed a broad endothermic peak at a temperature 128.99°C, a sharp endothermic peak at 219.33 and at 234.60°C it showed a sharp endothermic peak. The results are given in Table 5, it indicates that there were no drug and excipient interactions during the coating process. The DSC thermographic peaks are shown in Figures 8 to 13

Scanning electron microscopy analysis

Surface characteristics were evaluated by using SEM analysis for pure drug and the C11 which is an optimized formulation, results showed that surface photographs of optimized formulation C11 was smooth surfaced, even and uniform without surface cracks. The SEM photographs were exhibited in Figures 14 and 15.

In-vivo Pharmacokinetic Studies of Cevimeline HCl Fast Dissolving Films

The cevimeline HCl (oral solution) administered through oral route attained the peak plasma concentration (C_{max}) of 11.7 ng/mL, the maximum time required to reach C_{max} (t_{max}) attained at 15 minutes with a biological half-life of 0.1 hour. The AUMC_(0-t) values observed for cevimeline HCl oral solution was 54.1 ng-hr/mL. The pure drug shows mean residence time of 11.7 hours. The optimized formulation C11 administered as fast dissolving film attained peak plasma concentration (C_{max}) of 30.2 ng/mL and time required to achieve maximum concentration (t_{max}) at 15 minutes shows biological half-life of 4.9 hours, respectively. The area under plasma concentration versus time plot (AUC_(0-t)) values obtained for optimized C11 formulation was found to be 150.2 ng-min/mL. The mean

Table 6: *In-vivo* pharmacokinetics of cevimeline HCl fast dissolving film (C11)

Parameters	Optimized formulation C11 (mg/mL)				Cevimeline HCl (Oral solution)					
	1	2	3	Mean (N = 3)	S.D	1	2	3	Mean (N = 3)	S.D
C _{max} (mg/mL)	30.1	30.2	30.15	30.2	0.0	11.5	11.6	11.9	11.7	0.2
T _{max} (min)	15	15	15	15	0.0	15	15	15	15	0.1
T _{1/2} (hr)	4.287873	4.912818	5.557922	4.9	0.6	0.135537	0.150132	0.151569	0.1	0.0
AUC _(0-t) (ng·hr/mL)	150	150.375	150.35	150.2	0.2	53.25	53.975	55	54.1	0.9
AUMC _(0-t) (ng·hr* hr/ mL)	372.25	373.25	373.725	373.1	0.8	109.75	112.95	114.75	112.5	2.5
MRT (hr)	30.1	30.2	30.15	30.2	0.0	11.5	11.6	11.9	11.7	0.2

residence time for the optimized tablet formulations C11 was found to be 30.2 hours, respectively. These results indicated that optimized formulation C11 showed improved drug release in plasma by prolonging the (MRT) mean residence time with enhanced (AUC), values indicating the increased dissolution rate with rapid onset of action and shows increased bioavailability. The concentration of drug cevimeline HCl in plasma and its optimized formulation C11 were noted in Table 6 and shown in Figure 16.

CONCLUSION

Cevimeline HCl oral fast dissolving films prepared by using solvent casting method showed better flexibility of films and exhibited good characteristic properties of film with enhanced bioavailability. The formulation optimized C11 prepared by using polyvinyl pyrrolidone showed an average drug release of 99.91% within 5 minutes, which was preferable for rapid dissolution and absorption. The drug content on average was found to be 29.63 ± 0.5 , and showed good folding endurance, results indicated that there was no drug and excipient interaction in FTIR and DSC studies as exhibited the smooth surface in SEM analysis. Films of cevimeline HCl were prepared by using a solvent casting process which was suitable for the treatment of dry mouth symptoms related to Sjogren's syndrome. *In-vivo* studies of cevimeline HCl showed that the concentration of drug in plasma was extended by prolonging the mean residence time with an enhanced dissolution rate and rapid onset of action with increased bioavailability.

ACKNOWLEDGEMENT

The author expresses sincere gratitude to Dr. P. Shailaja, Associate Professor, Department of Pharmaceutical Technology, A.U College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, A.P, India, for providing valuable guidance to carry out the research work.

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