

**FORMULATION AND ESTIMATION OF ATOMOXETINE
HYDROCHLORIDE BUCCAL DRUG DELIVERY SYSTEM****Pragya Srivastava*¹ and Hema Jaiswal²**¹Research Scholar, Institute of Pharmaceutical Sciences and Research, Lucknow (UP) IN.²Associate Professor, Institute of Pharmaceutical Sciences and Research, Lucknow (UP) IN.Article Received on
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(UP) IN.**ABSTRACT**

As oral route is the preferred route of administration of majority of drugs but it has certain limitations such as presystemic metabolism or first pass metabolism in liver, g.i.t upset and destructions of enzymes. After gone through extensive review of literature, this research focuses on designing, development and estimation of atomoxetine hydrochloride buccal drug delivery system with different and suitable vehicles and plasticizers with different ratio of mixing and evaluation of same by following standard parameters. The buccal patch was formulated by most conventional method- solvent casting and evaluated for multiples of parameters such as surface pH, folding

endurance, flatness, moisture content, uniformity of contents, weight variations, in-vitro drug release and stability. In results, the formulated buccal patch demonstrated a significant buccal patch by following excellent form of patches characteristics. They all have seen of great purity because of strength of polymers used. In conclusion, it may be beneficial by the use in the market. It shows a significantly low investment of money. In future aspects, it may be applied for the treatment of various neurological and other aspects of diseases.

KEYWORDS: Atomoxetine hydrochloride, Buccal delivery system, ADHD, Conventional.**INTRODUCTION**

Buccal route is preferred route of administration of vast of drugs but it has certain limitations such as presystemic metabolism or first pass metabolism in liver, g.i.t upset and destructions of enzymes. To overcome such problems, a route came in knowledge that includes several as intranasal, buccal, transdermal and pulmonary routes that deliver the drugs in blood stream and bypass the presystemic metabolism (Verma et al. 2017). Bioadhesive medication

conveyance definitions were presented in 1947 when gum tragacanth blended in with dental glue powder to apply penicillin on oral mucosa. In later a longtime conveyance of helpful specialists by means of Mucoadhesive medication conveyance framework has gotten exceptionally fascinating. Certain drugs have absence of viability due to diminished bioavailability, g.i.t bigotry, capricious and unpredictable retention or pre-foundational end of other potential course for organization (Rao et al. 2013). Buccal preparations are made to allow sustained and localised therapy and tool for effective delivery (Smart, 2015). The ability to keep a movement system at a particular region for a sweeping time period has unbelievable interest for the two neighborhoods similarly as principal prescription bioavailability (Rao et al. 2013). Different materials from lipids to typical or designed polymers and others have been used to guarantee and pass on drugs in a kept up with, controlled or zeroed in on way, and overhaul their take-up through the buccal mucosa working on their bioavailability and healing outcome (Macedo et al. 2020). The mucosal covering of buccal cavity gives a lot milder climate to tranquilize ingestion. The Mucoadhesive controlled-discharge gadgets can work on the appropriateness of a medication by keeping up with the medication fixation between the successful and poisonous levels. Mucoadhesive qualities are a factor of both the bio-glue polymer and the medium in which the polymer will work (Patel et al. 2013). Chitosan is one of the common polymers, which is by and large broadly utilized. Chitosan is made out of glucosamine and N-acetyl glucosamine which are likewise constituent of mammalian tissue. It is non-harmful, biocompatible and biodegradable polymer. This polymer is considered for its film similarly as cross section molding limits. Chitosan is excessively used as protein inhibitor similarly as entrance enhancer properties (Rao et al. (2013). To improve buccal retention, a few methodologies have been presented. Expanded penetration of the medication through the buccal layer and counteraction of the medication debasement by chemicals was accomplished by modifying the physicochemical properties of drug (Reena, 2018). Despite the fact that the rectal, vaginal, and visual mucosa all offer certain benefits, the helpless patient agreeableness related with these destinations renders them saved for nearby applications as opposed to fundamental medication organization. (Mujoriya et al. 2011):

Gulping of spit can likewise conceivably prompt the deficiency of broke down or suspended medication and, eventually, the compulsory evacuation of the measurements structure. (Reddy et al. 2011).

The following table focuses on the selection of polymers according to their mechanism.

Table 1: Category of polymers.

S.N.	Category	Polymers
1.	Natural or Semi-synthetic	Agarose, chitosan, Guar gum, pectin, HEC, HPMC
2.	Synthetic polymers	Acrylic acid-based polymers (co-polymer of acrylic acid, PEG etc.)
3.	Hydrophilic	HPC, Sodium alginate
4.	Lipophilic	Chitosan
5.	Cationic	dextran
6.	Anionic	pectin, Sodium alginate etc.
7.	Co-valent	Cyanoacrylate
8.	Hydrogen bonded	Acrylates such as poly methacrylic acid
9.	Electro-static conjugation	Chitosan

Atomoxetine was initially named tomoxetine, with starting exploration finished for a sign of the treatment of significant despondency. Nonetheless, advancement of the medication for the treatment of wretchedness was ceased in 1990 for hazy reasons. In 1996, the prescription was re-introduced as a possible treatment for ADHD. (Ledbetter, 2006). Thus, expanding noradrenergic transmission in cortical regions is estimated to be identified with the adequacy of atomoxetine in ADHD (Corman et al. 2004).

Reddy, Rohit and Sunil (2019) have formulated and evaluated mucoadhesive buccal patches on atomoxetine. The patches were prepared using Eudragit-L100, HPMC K15M, and HPMC K4M polymers by solvent casting method.

After going through extensive review of literature, this research focuses on designing, development and estimation of atomoxetine hydrochloride buccal drug delivery system with different and suitable vehicles and plasticizers with different ratio of mixing and evaluation of same by following standard parameters.

MATERIALS AND METHODS

Experimental Requirements

Table 2. List of requirements.

S. No.	Chemical Supplier Category
1.	Atomoxetine HCl CDH Laboratory, New Delhi API
2.	Eudragit L 100 Zim Laboratories Limited, Kalmeshwar, Nagpur
3.	HPMCK 15L, Evonik Degussa India Private Limited, Mumbai
4.	Propylene Glycol 400, CDH Laboratory, New Delhi
5.	Ethanol, CDH Laboratory, New Delhi

Preformulation Studies

Preformulation studies performed before the commencement of formulation development, and the major goal of the study is to produce or develop stable, safe, and therapeutically effective and efficacious dosage forms that are mainly related to the characterization of the physicochemical properties of the drug substance.

Characterization of Atomoxetine

For preformulation studies, the micronized form of Atomoxetine Hcl was subjected to physical tests.

Identification of Drug

FT-IR spectroscopy (Fourier transform infrared spectroscopy) method was used for the identification and evaluation of drug and excipients. Drug KBR pellets were used to record the FT-IR spectrum with a Perkin-Elmer model.

FT-IR spectroscopy technique

FT-IR spectroscopy method was used for the evaluation of the drug, there were several stretching's observed between C-H, C-N, and C-O. For the scanning process, the pure form of the drug was used. The IR spectra were taken by mixing Potassium bromide with the drug. In FT-IR spectra the functional groups showing Characteristics peaks.

Protocol for Drug – Excipients Compatibility Studies

For the selection of suitable additives or excipients to develop a pharmaceutical formulation, the drug – excipients compatibility studies are most important. Various organoleptic properties were observed throughout this study. Drug excipients' compatibility test assures the stability of the formulation. The separate scanning was done for pure drug and drug with excipients in a particular ratio.

The active drug was mixed with Potassium bromide and spectra were taken. Accordingly, the excipient and Potassium bromide mixed in the same ratio i.e., 1:1 ratio and spectra were taken, the FT-IR spectrum of Atomoxetine was compared with FT-IR spectra of Atomoxetine with other excipients. Shifting or Disappearance of Atomoxetine peak in spectra was studied.

Procedure

Atomoxetine was mixed with various excipient used in the study in the ratio as given in table 0.0, then filled in glass vials along with low-density polyethylene stopper with holes in the

stopper and subjected to a different condition like room temperature, 60°C and 2-8°C for four weeks. After the completion of the specified period, blends were tested for their physical change and moisture content.

Proposed Formulations for Experiments

The formulation was prepared by using different concentrations of drug and respective polymers for better bioavailability and release of active pharmaceutical ingredient.

Required quantity of Ingredients

The following table depicts the quantity of ingredients required for formulation of requisite batches.

Table 3: Required quantity of Ingredients for experimental Batches (250 Buccal Patches for each batch).

Sr. No.	Ingredients	Approx. Quantity Required
1	Atomoxetine Hcl	0.025 kg
2	Edragit L100	1.250 kg
4	HPMCK 15M	1.250 kg
5	Propylene Glycol	0.625 Ltr.
7	Ethanol	3.750 Ltr.

Different ratios of excipients (F1-F5)

The following table represents the different ratios of excipients taken for the formulation of buccal patches-

Table 4: F1-F5 with different ratios of excipients.

Sr. No.	Ingredients	Unit Formula (mg or ml/tablet)				
		F-1	F-2	F-3	F-4	F-5
1	Atomoxetine Hcl (mg)	20	20	20	20	20
2	Propylene Glycol 400 (ml)	0.5	0.5	0.5	0.5	0.5
3	HPMC E 15 (mg)	45	50	55	60	65
4	Edragit L 100 (mg)	65	60	55	50	45
5	Ethanol (ml)	3	3	3	3	3
Net Wt. / Tab. in mg		140	140	140	140	140

Drug- Excipient compatibility study protocol

The following table depicts the drug excipient compatibility ratio-

Table 5: Drug- Excipient compatibility study protocol.

S. N.	Ingredients	Drug: Excipients Ratio
1	Eudragit L 100	1:1
2	HPMCK15L	1:1
3	Propylene Glycol	1:1
4	Ethanol	1:1

Formulation Development

The material and method required for the formulation of the Buccal Patches and the associated evaluation parameter of the latter are explained in the following section.

Method for the preparation of the Atomoxetine Buccal Patches

A total of 5 formulations were prepared using various steps. The different formulation prepared for Atomoxetine Buccal Patches is given in table.

The steps used in the preparation of Buccal Patches were as follows

Process involved during developmental stage of formulation

Molecular dispersion technique with micronized active drug Atomoxetine Hcl by using Natural super disintegrants, the process will be the same for every trial batch from Batch No. F1 – Batch No. F5 for the manufacturing of Buccal Patches.

First Step Process: - Material Sifting

Atomoxetine, Eudragit L 100, HPMCK 15L was accurately measured and shall be sifted through #40 separately. Propylene Glycol 400 and Ethanol was filtered through a filter cloth before use.

Second Step Process: - Manufacturing Process

The buccal patches of Atomoxetine were set up by dissolvable vanishing strategy. The framework type controlled buccal medication conveyance frameworks were set up by utilizing ethanol as dissolvable for HPMC and ethanol as dissolvable for Eudragit L 100. For the various bunches of definitions, the polymer arrangement in various extents were blended and mixed on attractive stirrer to give homogenous clear arrangement, drug was added gradually to the polymer arrangement and mixed altogether to acquire a uniform arrangement. Polyethylene glycol 400 (PEG 400) was added as plasticizer. The polymeric arrangement of medication was poured onto the mercury surface and covered with reversed pipe, then, at that point dried at room temperature in a residue free climate. After 24 h, the fix

was cut into 3 cm measurement. The measure of the medication needed in the petri dish is primarily relies on a superficial level space of the petri dish.

Third Step Process: - Analysis

Buccal Patches was analyzed as per the official guidelines for all parameters and a comparative study shall be done with the existing market brand.

Parameters fixed for the tablet

The following table depicts the parameters mixed for the final tablets obtained-

Table 6: Parameters fixed for the tablet.

Parameters	F1	F2	F3	F4	F5
(Weight) Variation	140.15±0.35	140.12±0.40	142.18±0.45	140.98±0.52	140.18±0.42
Thickness	0.76±0.40	0.77±0.64	0.81±0.60	0.82±0.55	0.80±0.50
Surface pH	6.25±0.25	6.22±0.23	6.5±0.18	6.48±0.30	6.18±0.38
Content Uniformity	20.58±0.01	19.56±0.01	19.77±0.02	19.86±0.02	20.76±0.02
Swelling Index	14	22	24	34	30
Mucoadhesion Time	3.40	3.48	3.50	4.05	3.91
Bioadhesive Strength	3.4	3.9	4.6	5.4	5.1
Folding Endurance	255	258	260	270	268

Formulation of buccal patches of atomoxetine (Solvent casting method)

Eudragit L100, HPMCK15M are weighed in specific ratios and they are dissolved in ethanol as solvent, using magnetic stirrer for proper solution. Atomoxetine (40mg), Propylene glycol and Tween 80 are added as permeation enhancer and plasticizer respectively to the above dispersion with continuous stirring. The uniform dispersion is poured in the petri plate. The rate of evaporation of solvent is controlled by inverting cut funnel over the patches. After 24h, the dried films are taken out and stored in desiccator to keep away from moisture.

Evaluation parameters (Tirunagari et al. 2014; Reddy et al. 2019).

Weight variation

The all the buccal patches will be determined for their weights and to compare among to make sure that these are under limits of weight variation.

Flatness

Each patch will evaluated for its flatness by both sides. Each patch will evaluated for its flatness by both sides. The length of each strip is measured and variation in the length

because the uniformity in flatness represents constriction, considering 0% constriction equivalent to 100% flatness.

Folding strength

The folding strength is measured manually for the buccal patch. A strip of the films is cut evenly and repeatedly folded at the same place until it is broken-out.

Moisture content

The patches are weighed individually and kept in a desiccator for 24 h. The patches are reweighed until a constant weight is obtained. Moisture content is calculated in percentage based on the difference between the initial and the constant final weights by using following formula-

$$\text{Percentage moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Drug content determination

A small area of patch is cut and dissolved in PBS solution at pH 7.4. Then the solvent ethanol is added to make polymer soluble and the remaining volume is made up to 100 ml with PBS (pH 7.4). Then 1 ml is withdrawn from the solution and diluted again up to 10 ml. The absorbance of the solution is taken at wavelength 270 nm and concentration is calculated.

Stability studies

Stability studies are carried out by keeping the optimized formulations in the butter paper and covered by aluminum foil and placed in it. It is sealed by heat at the end for one month at room temperature. The films are taken at different time intervals like 0 to 4th week and are analyzed for its appearance, disintegration time and drug content by following above mentioned protocols.

RESULTS AND DISCUSSION

Characterization of Active Drug

The active drug was evaluated for various parameters through the standard test and accordingly the results have been mentioned in the following table.

Table 7: Result analysis of Atomoxetine Hcl.

Test	Specification	Observation	Conclusion
Description	White color powder	White color powder	Complied
Odor	Odorless	Odorless	Complied
Solubility	Highly soluble in water	Practically Highly soluble in water	Complied
	Partially soluble in methanol	Practically partially soluble in methanol	Complied

API- Excipient compatibility test

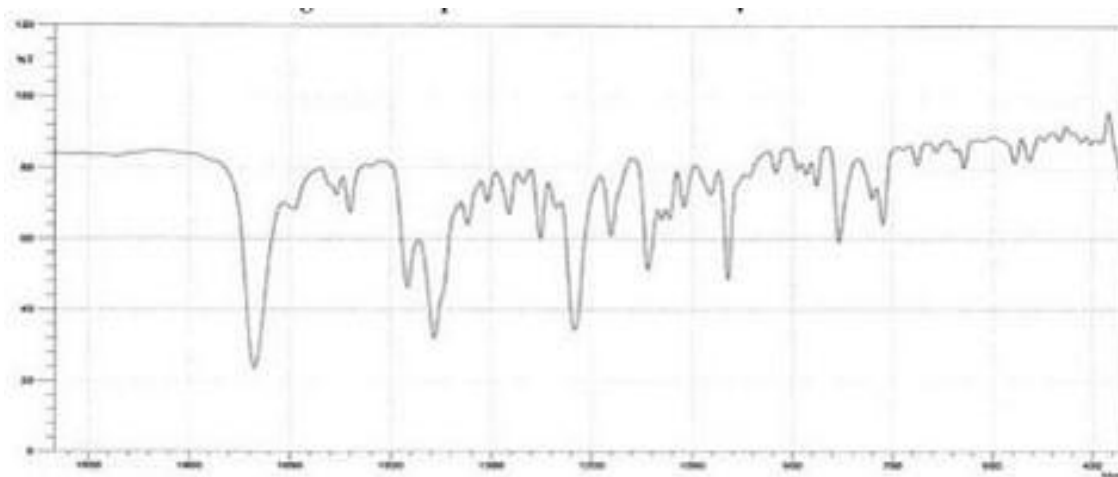
The API was evaluated along with every excipient for compatibility studies and the results were recorded as per the data obtained after completion of the studies in the following table-

Table 8: Drug-excipient compatibility data.

Drug+ Excipient	Storage Conditions for 1 ½ months		
	Room Temperature	Hot air oven	Freezing Temperature
Atomoxetine (Api)	Stable	Stable	Stable
Api + Eudragit L	Stable	Stable	Stable
Api + Hpmck 15 L	Stable	Stable	Stable
Api + Propylene Glycol	Stable	Stable	Stable
Api + Ethanol	Stable	Stable	Stable

FT-IR Spectrum for Drug Excipients Study**FT – IR spectrum of Atomoxetine HCL**

Fourier change FT-IR utilizes the numerical cycle to interpret the crude information into real range. FT-IR technique is used to acquire the infrared range of transmission or retention of a fuel test. The infrared assimilation range $600\text{--}4000\text{cm}^{-1}$. the particular sub-atomic gatherings winning in the example will be resolved through range information in the computerized programming of spectroscopy. The following table 3.3.1 depicts the FT-IR spectrum of atomoxetine Hcl (Shameer & Nishath, 2019).

**Fig. 1: FT – IR spectrum of Atomoxetine HCL.**

FT – IR Spectrum of API + Eudragit L100

FT-IR range is recorded some place in the scope of 4000 and 400 cm^{-1} . For FT-IR assessment, the polymer was deteriorated in chloroform and layered on a NaCl valuable stone and after scattering of chloroform, the polymer film was presented to FT-IR. The scope of PHB shows maximum at 1724 cm^{-1} and 1279 cm^{-1} , which looks at to unequivocal pivots carbon particles. The top at 1724 cm^{-1} identifies with C–O stretch of the ester bundle present in the nuclear chain of especially mentioned plan and the adsorption band at 1279 cm^{-1} thinks about to ester holding (Sindhu, Vinod, Pandey, 2015). The following table 3.3.2 depicts the FT-IR band of atmoxetine Hcl.

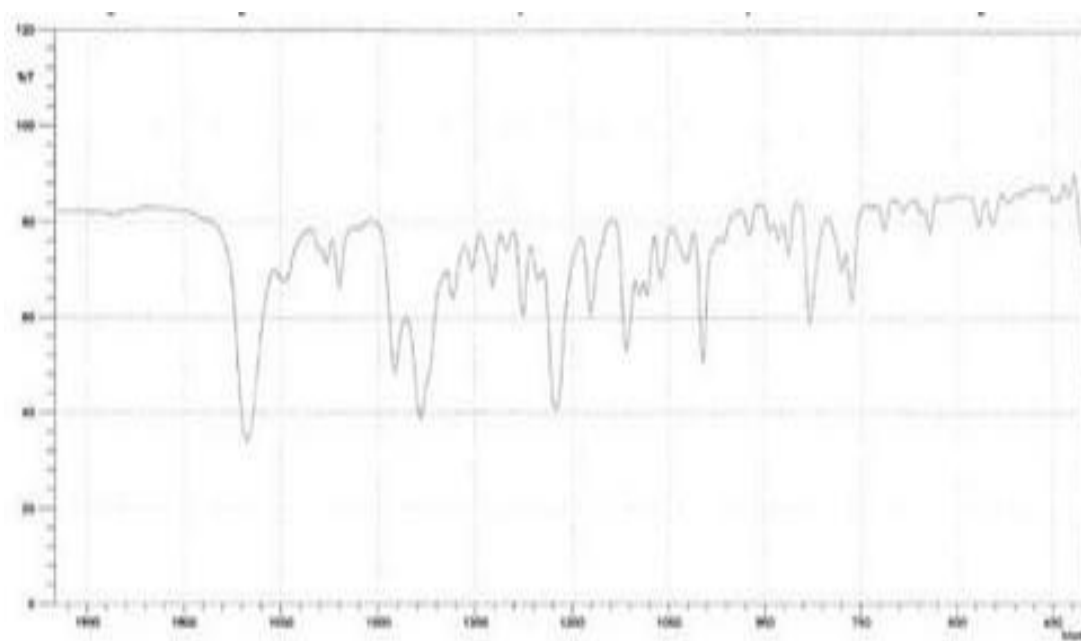


Fig. 2: FT – IR band of API + Eudragit L100.

FT – IR Spectrum of API + HPMCK 15 L

FT-IR technique is used to acquire the infrared range of transmission or retention of a fuel test. The infrared assimilation range 600–4000 cm^{-1} , the particular sub-atomic gatherings winning in the example will be resolved through range information in the computerized programming of spectroscopy (Shameer & Nishath, 2019).

The following table 3.3.3 depicts the FT-IR spectrum of API + HPMCK 15 L.

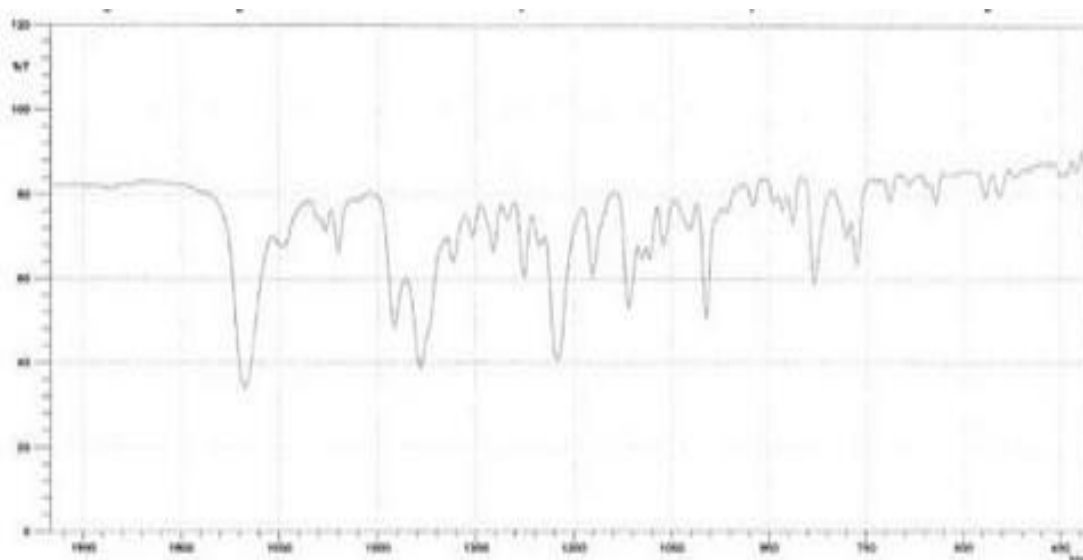


Fig. 3: FT – IR Spectrum of API + HPMCK 15 L.

FT – IR Spectrum of API + Propylene Glycol

It is utilized to distinguish distinctive practical gatherings in PHB. FT-IR range is recorded somewhere in the range of 4000 to 400 cm^{-1} . For FT-IR assessment, the polymer was broken down in chloroform and layered on a NaCl valuable stone and after dissemination of chloroform, the polymer film was presented to FT-IR. The scope of PHB shows tops at 1724 cm^{-1} and 1279 cm^{-1} , which thinks about to unequivocal pivots carbon particles. The top at 1724 cm^{-1} identifies with C–O stretch of the ester pack present in the nuclear chain of especially mentioned plan and the adsorption band at 1279 cm^{-1} looks at to ester holding (Sindhu, Vinod, Pandey, 2015).

The following table 3.3.4 depicts the FT-IR band of API + Propylene Glycol.

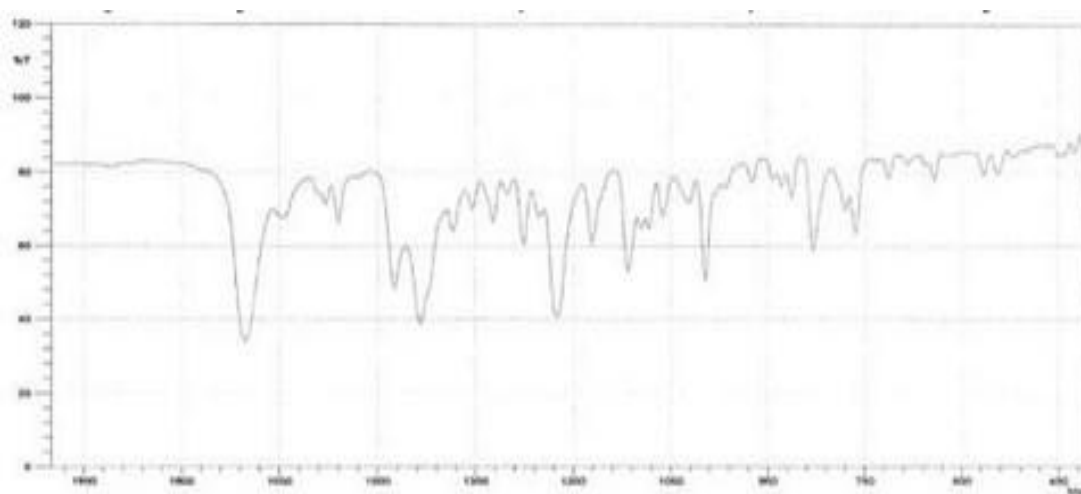


Fig. 4: FT – IR Spectrum of API + Propylene Glycol.

FT – IR Spectrum of API + Ethanol

FTIR technique is utilized to acquire the infrared range of transmission or retention of a fuel test. The infrared assimilation range $600\text{--}4000\text{ cm}^{-1}$, the particular sub-atomic gatherings winning in the example will be resolved through range information in the computerized programming of spectroscopy (Shameer & Nishath, 2019).

The following table 3.3.5 depicts the FT-IR band of API + Ethanol.

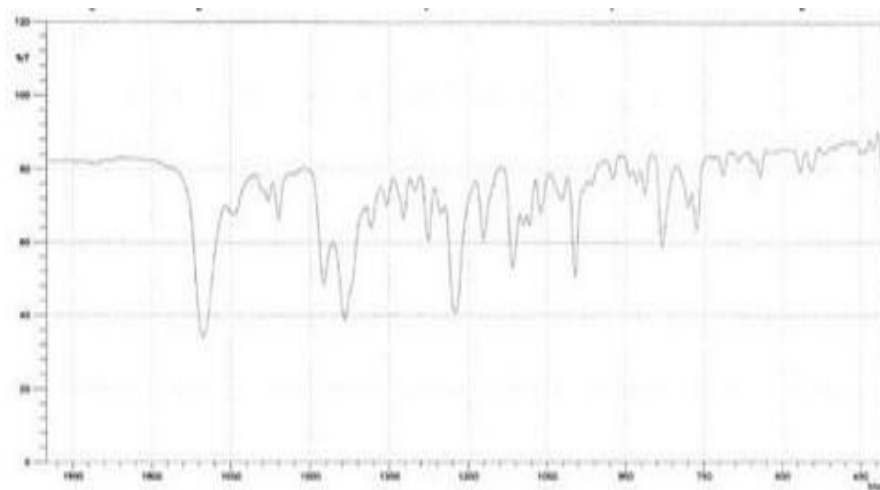


Fig. 5: FT – IR Spectrum of API + Ethanol.

Preparation of Atomoxetine stock solution (100µg/ml) in 0.1N HCL (IP, 2018)

The drug (Atomoxetine) 100 mg was completely dissolved in some quantity of 0.1N hydrochloric acid in 100 mL capacity beaker.

Determination of λ_{max} (maximum absorption)

Max. Absorbance (λ_{max}) of Atomoxetine was estimated by UV (visible spectrophotometer) by scanning drug samples at λ 270 nm and spectra were found.

2. Evaluation of Buccal Patches

Surface pH study

The following table depicts the surface pH of the prepared buccal patch. The pH was estimated by the digital pH meter of laboratory configuration.

Table 9: Surface pH of prepared buccal patch.

Formulation	Time (checked after)	pH
F1	1 hour	7.2
F2	1 hour	6.8
F3	1 hour	6.8

F4	1 hour	7.3
F5	1 hour	6.7

Folding endurance

The following table shows that formulations from F1- F5 exhibits an optimum level of folding power-

Table 10: Folding power.

Formulation	Folding endurance
F1	19
F2	22
F3	27
F4	29
F5	23

Swelling index study

The following table shows the swelling power the formulations (F1- F5)-

Table 11: Swelling power.

Formulation	Weight (g)	Weight after swelling
F1	0.82	0.91
F2	0.75	0.82
F3	0.69	0.76
F4	0.79	0.85
F5	0.73	0.85

Determination of in-vitro release time

The following table represents the in-vitro release time

Table 12: Cumulative % drug release.

Time (hr)	Cumulative % drug release				
	F1	F2	F3	F4	F5
1	6.24± 0.45	6.90± 0.34	7.50± 0.29	7.85± 0.41	7.13± 0.37
2	8.10± 0.51	8.24± 0.47	8.41± 0.57	9.23± 0.53	9.31± 0.46
3	11.42± 0.72	11.71± 0.79	10.90± 0.63	11.72± 0.82	11.12± 0.48
4	13.26± 0.61	13.71± 0.57	13.91± 0.51	14.17± 0.63	13.32± 0.84
5	17.81± 0.60	17.21± 0.30	16.87± 0.73	17.49± 0.52	17.10± 0.48

Measurement of muco-adhesive strength

Table 13: Mucoadhesive strength.

Preparation	F1	F2	F3	F4	F5
Muco-adhesive Strength (G)	3.41	3.91	4.20	3.52	4.13

Folding endurance

The above formulated buccal patch demonstrated a rigid folding endurance in the aspect of folding ability of the patch. It can be kept under some strong mechanical pressure and thrush. Its better folding endurance enables it- durable & long lasting in terms of stability.

Swelling index study

The above formulated buccal patch showed an adequate swelling proportion. Swelling index plays a significant role in the physical characteristics of buccal patch. It confirms about its better drug release and dissolution rate in the medium of saliva. This allows the formulation a good bioavailability in the systemic circulation after get absorbed.

In-Vitro release time

The buccal patch showed an excellent in-vitro release rate of the formulation. It assures a uniformity of the contents as well. This characteristic of the formulation is essential to be proved as fast release oral films in an appropriate time. The release time of buccal patch depends on the uniformity of patch and favorable environment for the drug release and dissolution.

Muco-adhesive strength

The mucoadhesive strength of the formulated patch showed a remarkable power due to incorporation of a variety of mucoadhesive polymers. It also helps in the development of stability of the formulation. It also facilitates the release of the Active Pharmaceutical Ingredient (API) with different polymers and excipients in the respective solvent medium.

Stability study

The patch was tested for stability of its form. It showed better stability of the formulation and it may because of strong polymers used with excipients. The main aspect for any formulation is to validate its stability because it declares the total life (shelf life) of the product formulated under ideal conditions. It was found stable because of the high-quality polymers were taken in the development of the product (buccal patch).

CONCLUSION

Buccal Patches of Atomoxetine were formulated to have the adequate mechanical strength to withstand during their handling, packaging, shipping, storage, and transportation. The tablets were prepared following the standards as prescribed by guidelines. Formulation F1 were

showing fast disintegration and dissolution profile. Drug dissolution further impact on bioavailability and therapeutic effect of formulation. The optimized formulation was considered for stability studies. The data obtained from stability studies demonstrated that Buccal Patches of Atomoxetine were steady and stable under various natural environmental storage conditions.

Mouth dissolving film of atomoxetine HCl was defined sufficiently. It showed a decent in vitro scattering time alongside rich appearance and other actual attributes like elasticity, % lengthening, collapsing perseverance. F2 was chosen dependent on its outcomes on performed assessment which were all ideal and furthermore had great mechanical properties. Accordingly, it very well may be a decent option to traditional Atomoxetine HCl tablets or containers (Tirunagari et al. 2014).

Buccal Patches (Buccal Patches) drug-delivery systems were developed for patient compliance, especially for pediatric, geriatric, dysphagia, tremor, or physically disabled and travelers. Sometimes it is impractical to access water which is required to administer the drug in the form of a tablet or capsules. (Kulkarni et al. 2010).

The various studies have been done by various researchers for the development of fast dissolving oral films to improve therapeutic effectiveness of drugs (Adhikari et al. 2010).

This research concerns with New Drug Delivery System (NDDS) that enhances the new approach in frequent dermal delivery of buccal drug delivery system of atomoxetine. It would be very impactful with easier, adequate sustained dosing at the site where absorption is rapid and specialized.

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