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DESIGN AND DEVELOPMENT OF MUCOADHESIVE DRUG DELIVERY SYSTEM OF MONTELUKAST SODIUM

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ABSTRACT
The Montelukast sodium is a leukotrine receptor antagonist used for the maintenance treatment of asthma, chronic asthma attacks and to relieve symptoms of seasonal allergies. The biological half life of montelukast sodium is 2.5 to 5.5 hrs and poor bioavailability upto 64%. Because of poor bioavailability of montelukast sodium by oral route, there is a need to increase its bioavailability by formulating it into buccal dosage forms. Hence, montelukast sodium is a suitable drug for buccal dosage forms and may provide a better therapeutic profile than oral route. In the present piece of research work, montelukast sodium buccal films were prepared using different mucoadhesive polymers like hydroxy propyl methyl cellulose (5 cps), Eudragit RL-100, poly vinyl pyrrolidone K-30, and different grades of carbopol (like carbopol-934, carbopol-940, carbopol-971 P and carbopol-974 P) by solvent casting technique. Buccal films were characterized for number of parameters like physical appearance and surface texture, weight uniformity, thickness, folding endurance, swelling index, surface pH, *in vitro* residence time, drug–excipients interaction study, drug content uniformity and *in vitro* drug release study. FT-IR studies revealed that, there was no interaction between drug and excipients used. From this study it was concluded that the film containing 5 mg of montelukast sodium were prepared by using eudragit RL 100 with hydroxy propyl methyl cellulose, hydroxy propyl methyl cellulose with carbopol 934, and hydroxy propyl methyl cellulose with carbopol 940 (F3, F4, and F5 formulations) were best formulations. Hence these formulations of montelukast sodium mucoadhesive buccal films promising one as the controlled drug delivery, shows moderate swelling, convenient resident time will lead to improve the bioavailability and greater therapeutic efficacy.

KEYWORDS: Montelukast sodium, eudragit RL-100, hydroxy propyl methyl cellulose, poly vinyl pyrrolidone, buccal film, *in-vitro* release.

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INTRODUCTION

The interest in novel rout of drugs administration occurs from their ability to enhance the bioavailability of the drugs impaired by narrow absorption windows in the gastrointestinal tracts. Drugs delivery via the buccal routs using bioadhesive dosage forms offer such a novel routs of drugs administration. This route has been used successfully for the systematic delivery of number of drugs candidates[1-5]. Problems such as high first pass metabolisms and drugs degradation in the gastrointestinal tract can be circumvented by administrating the drug buccal routes[6,7]. Moreover, buccal drug delivery offers safe and easy method of drugs utilization, because drug absorption can be promptly terminated in case of toxicity by removing buccal dosage form from buccal cavity.

Substantial efforts have recently been focused upon placing a drug or drug delivery system in a particular region of the body for extended period of time. This need is not only for local targeting of drugs but also for a better control of systemic drug delivery[8]. Mucoadhesive drug delivery systems are delivery systems, which utilize the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting of drug to particular region of the body[9].

The montelukast sodium (MS) is a leukotrine receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies[10]. The main drawback of

conventional MS formulation is that it undergoes hepatic first pass metabolism. Thus, it shows plasma or biological half-life 2.5 to 5.5 hrs[11], thereby decreasing bioavailability up to 64% [12]. The present work describes such delivery system, which will improve the biological half-life as well as bioavailability of MS. In the present research work, MS buccal films were prepared using different mucoadhesive polymers like hydroxy propyl methyl cellulose (HPMC) (5 cps), Eudragit RL-100, poly vinyl pyrrolidone (PVP) K-30, and different grades of carbopol (CP-934, 940, 971 P, and 974 P) by solvent casting technique. The prepared buccal films were characterized for different parameters.

MATERIALS AND METHODS

MS was obtained as gift sample from Morepen Pharma. Pvt. Ltd., Solan (Delhi). Eudragit RL-100 was obtained as gift sample form Evonik Pharma Pvt. Ltd., Mumbai. Carbopol 971 P (CP 971P) and carbopol 974 P (CP 974P) were obtained as gift sample from AstraZeneca Pharma India Ltd, Bangalore. HPMC (5 cps), propylene glycol (PG), and PVP K-30 were purchased from S.D. Fine Chem. Ltd., Mumbai and Himedia Chem. Lab., Mumbai respectively. Carbopol 934 (CP 934) and carbopol 940 (CP 940) were purchased from S.D. Fine Chem. Ltd., Mumbai.

Preparation of the films

Buccal films of MS were prepared by solvent casting technique employing mercury as substrate [13]. Compositions of circular cast films of various formulations are mentioned in **Table 1.** The mucoadhesive films were prepared using polymers like HPMC (5 cps), different grades of CP, Eudragit RL-1OO and PVP K-30. PG was used as plasticizer. The calculated amount of polymer was dispersed in three fourth volume of water with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. In case of Eudragit RL-100 containing films, a polymer was firstly dissolved in ethanol (95%) with continuous stirring[14]. The calculated amount of MS was incorporated in the polymeric solutions after levigation with 0.1ml of PG. The solution was casted onto mercury substrate then kept in hot air oven at 40^0 for 24 h. All the films were dried and cut into size 10 mm, each film containing 5 mg of MS and were packed in aluminum foil. The 10 mm MS films are shown in **Fig1**.

Evaluation of Mucoadhesive Buccal films

The prepared buccal films were evaluated for different properties: Physical properties like weight uniformity, thickness, folding endurance, swelling index, surface pH, and mechanical properties like *in-vitro* residence time, bursting strength of films and evaluation of MS films like drug content, *in-vitro* release study and FTIR studies.

Appearance of the film was evaluated by observing the color, elegance, stickiness and texture. Weight uniformity of the 10 mm film was measured using electronic balance. Three films of the size 10 mm diameter were weighed individually and the average weights were calculated[15,16]. The thickness of each film was measured using screw gauge with a least count of 0.01 mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken[16,17]. The weight uniformity and thickness of all formulations was recorded (n=3). The flexibility of films can be measured quantitatively in terms of folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately two cm^2) at the same place until it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance[18]. The folding endurance and percent swelling index of films are carried out for three times.

Weight and area increase due to swelling were measured[19,20].

Weight increase due to swelling: A drug-loaded patch of two cm^2 was weighed on a preweighed cover slip. It was kept in a petridish and 50 ml of water was added. After every 5 min, the cover slip was removed, wiped with tissue paper, and weighed upto 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

Area increase due to swelling: A drug loaded patch size of two cm^2 was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. After determination of the original film weight, the samples were allowed to swell on the surface of agar plate kept in a hot air oven maintained at 37^0. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling, % S, was calculated using the following equation:

$$\% S = \frac{Xt - Xo}{Xo} x\ 100$$

Where, Xt is the weight or area of the swollen patch after time t and X_0 is the original patch weight or area at zero time.

Surface pH was measured by placing three films of each formulation were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min[21]. A mean of three reading was recorded (n=3). *In-vitro* residence time[22] was

determined using USP disintegration apparatus. The disintegration medium was 800ml of 0.5% SLS solution maintained at 37 ± 2^0. The segments of rat intestinal mucosa, each of three cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three mucoadhesive films of each formulation were hydrated on one surface using 0.5% SLS solution and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the 0.5% SLS solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the films from the mucosal surface was recorded (n=3). A test for measuring the resistance of films to bursting and reported in kilo-Pascal or pounds per square inch or Kg/cm^2. The burst strength of all the films was evaluated by using standard bursting strength tester **(Fig 2)**. The films were tested for drug content uniformity by UV-Spectrophotometric method. Films of 10 mm diameter were cut from three different places from the casted films[23]. Each film was placed in 100 ml volumetric flask and dissolved in 0.5% SLS solution and 5 ml is taken and diluted with 0.5% SLS solution up to 10 ml. The absorbance of the solution was measured at 342 nm using UV/visible spectrophotometer (Shimadzu UV-1700). The percentage drug content was determined using the standard graph and the same procedure was repeated for three films (n=3). *In-vitro* release studies were carried out by attaching sigma dialysis membrane to one end of the open cylinder, which acts as donor compartment. The prepared buccal films containing drug was placed inside donor compartment, which is, agitated continuously using magnetic stirrer and then temperature was maintained at 37 ± 1^{0} [24]. Receptor compartment consists of 100 ml of 0.5 % SLS solution, sample of 2 ml were withdrawn at periodic intervals from receptor compartment and replaced with fresh 2 ml of 0.5 % SLS solution immediately and the drug release was analyzed spectrophotometrically at 342 nm. Release rate was studied for all designed formulations.

RESULT AND DISCUSSION

Mucoadhesive films of MS were prepared using mucoadhesive polymers HPMC (5 cps), different grades of CP, PVP K-30 and Eudragit RL-100. PG was used as the plasticizer and as well as penetration enhancer. All the films were shows smooth surface and elegant texture. The films were characterized for their physical characteristics, surface pH, thickness, folding endurance, drug content uniformity, percent swelling index and release characteristics are given in **Table 2**. The film weights of 10 mm film was found to be in the range of 32.33 ± 1.152 to 37.66 ± 0.576 mg and film thickness was observed to be in the range of 0.253 ± 0.016 to 0.353 ± 0.020 mm.

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymer, the surface pH of the buccal films was determined to optimize both drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close to buccal / salivary pH as possible, by the proper selection of the polymer for developing the buccal films. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of different films.

The folding endurance was measured manually, by folding the film repeatedly at a point till they broke. The breaking time was found to be highest for F7 (286 ± 3.464) and lowest for F3 (260 ± 1.000). It was found that folding endurance of HPMC films was increased by the addition of polymers in the order; PVP K-30, CP-940, CP-934, CP-971P, CP-974P and decreased by addition of Eudragit RL-100. The folding endurance values of the films were found to be optimum and therefore the films exhibited good physical and mechanical properties. **Fig 3** shows the results of percent swelling index. The comparative percentage swelling behaviors for various formulations were given in **Table2.** The percentage swelling of HPMC (5 cps) films was reduced by addition of different grades of carbopol and eudragit RL-100 and increased by the addition of PVP K-30. The PVP K-30 containing films showed higher percent swelling due to freely soluble in water. The water-soluble hydrophilic additive dissolves rapidly resulting in high porosity. The incorporation of PVP K-30 induced significant reduction of *in-vitro* residence time of the studied formulae, which may correlate with the increase in swelling behavior due to enhanced erosion rate. The *in-vitro* residence time was determined using USP disintegration apparatus. *In-vitro* residence time of the film was in the range of 3.13 ± 0.151 to 5.43 ± 0.057 hrs. The *in-vitro* residence time of the mucoadhesive polymers are observed as given in **Table 2**. The drug content in formulations was uniform with the range of 94.33 ± 1.175 to 96.33 ± 1.001 %. On the basis determination, it was considered that the drug was dispersed uniformly through out the film. The bursting strength of films is in the range of 4.366 ± 0.267 to 5.93 ± 0.057 Kg/cm^2. The percentage drug content uniformity and bursting strength results of all formulations are given in **Table 2.** The *in-vitro* release studies of various formulations were performed in 0.5% SLS solution at 342 nm. Distinguishable difference was

observed in the release pattern of MS film containing different grades of CP, PVP K-30 and Eudragit RL-100 in graph plotted between the cumulative percent drug released from the formulation and time **(Fig 4)**. During diffusion, PVP K-30 containing films swelled forming a gel layer on the exposed film surfaces. The loosely bound polymer molecules in these films were readily eroded, allowed the easy release of MS as compared to different grades of CP and Eudragit RL-100. After 8 h the release was found in the range of 74.24 - 93.62 % in all formulations.

Kinetics drug release results were given **Table 3** and shown in **Figs 4-5**, correlation coefficient (r^2) values are significantly correlation (99% probability level) was found and also coefficient (r^2) values are higher than that of first-order release kinetics. It may be concluded that release kinetics followed zero order. Mechanism of drug release pattern i.e. diffusion and swelling was confirmed by Higuchi plots. **(Fig 6)** shows the graphical representation of cumulative percentage drug release versus square root of time. The Higuchi plots were found to be linear with correlation coefficient values were given in **Table 3.** It was concluded that the release of drug from the films followed the diffusion-controlled mechanism in all the formulations. The plots of log cumulative percentage drug release versus log time were found to be linear to the all formulations. From **Fig 7**, it is concluded that the release of MS from films have obeyed Super Case- II transport. The correlation coefficient values of Peppas plot were given in **Table 3**.

The IR **(Fig 8)** spectrum of pure drug MS exhibited has a broad band around 3411 cm^{-1} indicating overlapping of these peaks. The peaks due to the C-H peaks have appeared as shoulders between 2900 cm^{-1} to 3100 cm^{-1}. The C=O peak has appeared at 1636 cm^{-1} along with a merged peak at 1613 cm^{-1}. This is due to the complex structure of the drug molecule. In formulation F3 is supervised to notice that in this case no change has been observed in IR spectra. Suggesting that characteristic absorption peaks are remained unaffected in the F3 formulation. The formulation F4 was prepared by using CP 934, HPMC and drug. In this case viscosity of CP is in the range of 29000 to 39000. To know exactly what the nature of formulation spectral measurement is carried out. The present of distinct carbonyl peak around 1620 cm^{-1} indicating that carbonyl group of drug has remaining intact and also distinct OH peak has been observed at 3400 cm^{-1} which may be due to the OH group of drug molecule. These data along with the aromatic C-H peak observed at 2900 cm^{-1}. Suggesting that drug has remained intact without undergoing any chemical change. However weak absorption peak of OH may be due to the drug has undergone hydrogenic bonding with excipients. Hence this is not a chemical product simple formulation. In formulation F5 shows same absorption peaks a little change in the nature of IR spectrum of resulting formulation has no effect during the formulation. The formulated product obtained exhibited IR spectrum almost at the same range.

CONCLUSION

From this study it was concluded that the film containing 5 mg of MS were prepared by using eudragit RL 100 with HPMC, HPMC with CP 934, and HPMC with CP 940 (F3, F4, and F5 formulations) were best formulations. Hence these formulations of MS mucoadhesive buccal films showing promising results as the controlled drug delivery, moderate swelling, convenient resident time, will lead to greater therapeutic efficacy, and improve the bioavailability.

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Table 1: Composition of different Mucoadhesive buccal films of MS

Ingredients	Formulation code						
	F1	F2	F3	F4	F5	F6	F7
MS (mg)	31	31	31	31	31	31	31
HPMC (mg)	960	960	960	960	960	960	960
PVP-K30 (mg)	---	60	---	---	---	---	---
Eu RL-100 (mg)	---	---	60	---	---	---	---
CP-934 (mg)	---	---	---	60	---	---	---
Ethanol (95%) (ml)	---	---	04	---	---	---	---
Propylene glycol (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Each 10 mm film contains 5 mg of MS, HPMC - Hydroxy propyl methyl cellulose (5cps), PVP K-30- Poly vinyl pyrrolidone K-30, Eu RL-100 - Eudragit RL-1OO, and Carbopol

Table 2: Physical evaluation of Mucoadhesive buccal films of MS

FC	Weight (mg)	Thickness (mm)	Surface pH	Folding endurance	% Swelling index	*in-vitro* residence time(h)	% Drug content	Bursting strength
F1	34.66 ± 1.526	0.253 ± 0.016	6.83 ± 0.057	266 ± 2.000	36.43 ± 2.426	3.40 ± 0.100	94.66 ± 1.545	5.233 ± 0.251
F2	37.33 ± 1.154	0.263 ± 0.005	6.76 ± 0.152	277 ± 3.460	43.48 ± 0.606	3.13 ± 0.151	94.33 ± 1.175	5.033 ± 0.378
F3	37.66 ± 0.576	0.253 ± 0.016	6.06 ± 0.152	260 ± 1.000	31.63 ± 3.095	5.43 ± 0.057	96.33 ± 1.001	4.366 ± 0.267
F4	33.66 ± 1.152	0.343 ± 0.011	6.56 ± 0.057	281 ± 3.605	33.57 ± 1.484	4.27 ± 0.025	95.05 ± 0.355	5.73 ± 0.057
F5	32.33 ± 1.152	0.353 ± 0.020	6.30 ± 0.100	280 ± 2.645	32.93 ± 1.345	5.06 ± 0.110	95.23 ± 0.880	5.93 ± 0.057
F6	34.33 ± 1.527	0.323 ± 0.015	6.46 ± 0.057	282 ± 3.000	36.21 ± 1.637	3.58 ± 0.102	95.17 ± 2.403	5.46 ± 0.152
F7	35.00 ± 2.000	0.346 ± 0.005	6.46 ± 0.152	286 ± 3.464	35.12 ± 1.739	4.15 ± 0.100	95.99 ± 2.646	5.66 ± 0.251

Formulation code: FC
Note: Values in parenthesis are standard deviation (±SD)

Table 3: Kinetic parameters of MS buccal films

Formulation code	Zero-order (r^2)	First-order (r^2)	Highuchi plot (r^2)	Peppas plot (r^2)
F1	0.9755	0.8143	0.9053	0.9638
F2	0.9909	0.8271	0.9426	0.9853
F3	0.9674	0.8707	0.9095	0.9863
F4	0.9913	0.9283	0.9439	0.9875
F5	0.9896	0.9226	0.9398	0.9889
F6	0.9952	0.9311	0.9538	0.9905
F7	0.9942	0.9343	0.9501	0.9894

Note: All the values are mean of three observation

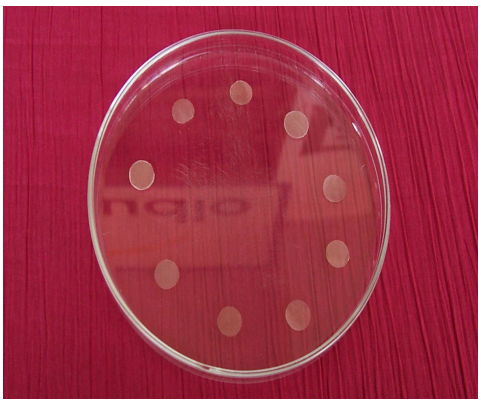

Fig 1: 10 mm buccal films containing MS

Fig 2: Bursting strength tester

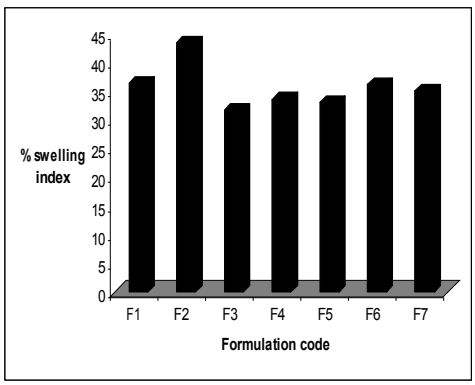

Fig 3: percentage-swelling index of different MS film formulations

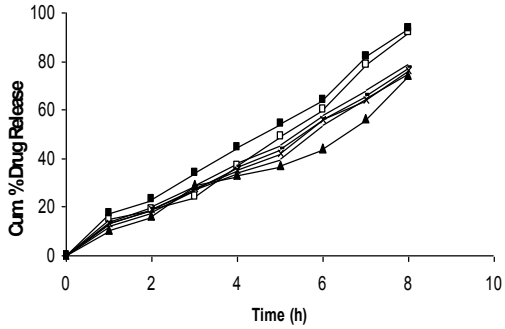

Fig 4: Comparative *in-vitro* drug release profiles of formulations F1 to F7.
In-vitro drug release was determined in 0.5% SLS solution from formulations F-1 (-□-), F-2 (-■-), F-3 (-▲-), F-4 (-×-), F-5 (-○-), F-6 (-●-), and F-7 (..-..) .

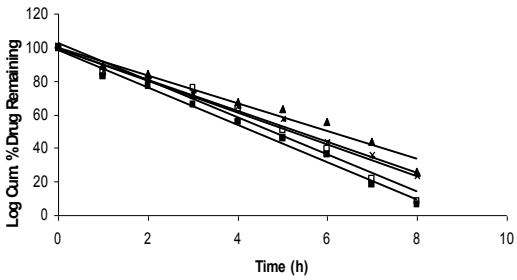

Fig 5: Log cumulative drug remaining of different formulations. F-1 (-□-), F-2 (-■-), F-3 (-▲-), F-4 (-×-), F-5 (-○-), F-6 (-●-), and F-7 (..-..) .

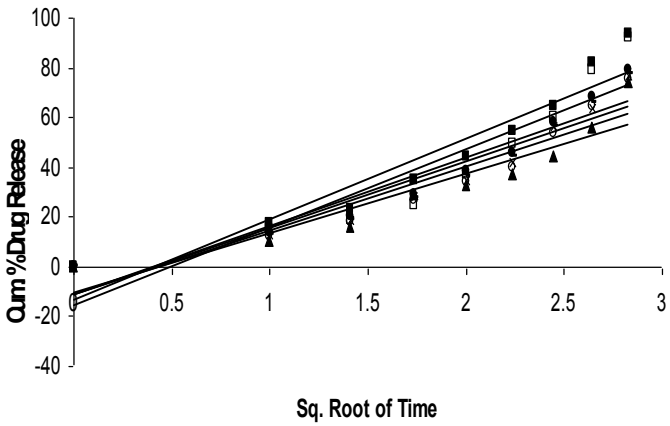

Fig 6: Higuchi plot of different formulations F-1 (-□-), F-2 (-■-), F-3 (-▲-), F-4 (-×-), F-5 (-○-), F-6 (-●-), and F-7 (..-..) .

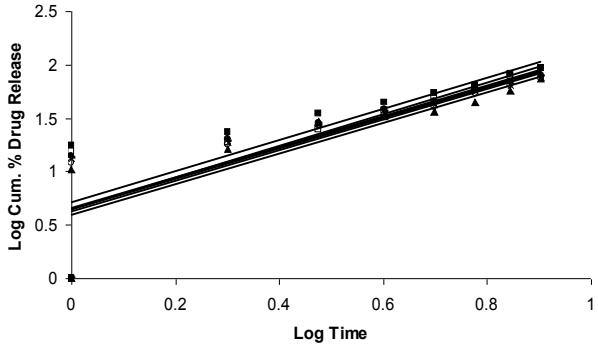

Fig 7: Peppas plot of different formulations F-1 (-□-), F-2 (-■-), F-3 (-▲-), F-4 (-×-), F-5 (-○-), F-6 (-●-), and F-7 (..-..) .

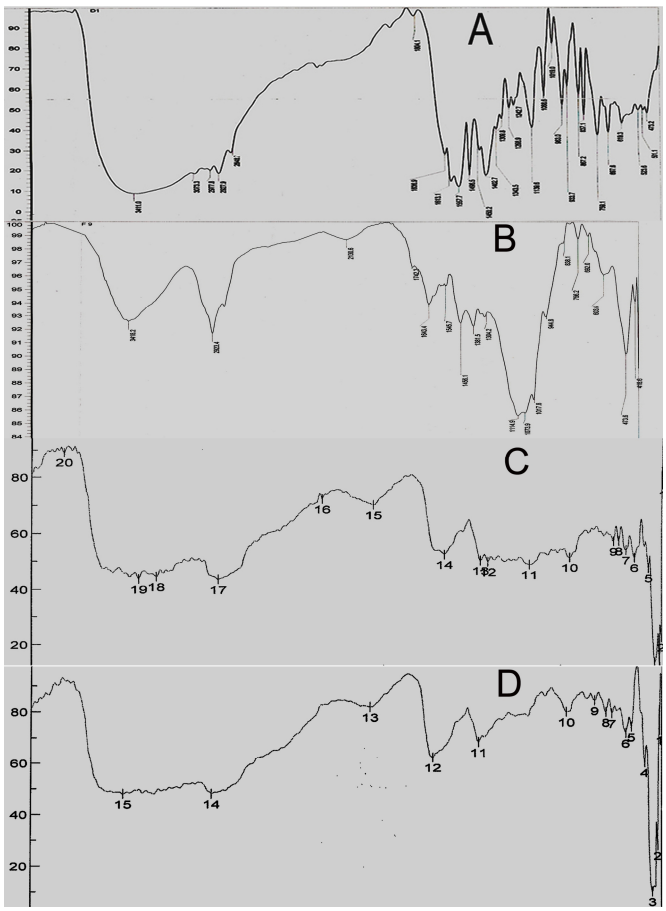

Fig 8: A- FTIR spectra of pure drug MS, B- FTIR spectra of formulation F3, C- FTIR spectra of formulation F4, and D- FTIR spectra of formulation F5.

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