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DESIGN AND INVITRO CHARACTERIZATION OF BUCCO-ADHESIVE DRUG DELIVERY SYSTEM: NEFOPAM HYDROCHLORIDE

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ABSTRACT

Nefopam is effective for prevention of shivering during surgery or recovery from surgery, significantly more effective than aspirin as an analgesic with a greater incidence of side effects such as sweating, dizziness and nausea, especially at higher doses. The buccal region, mucosal cavity of the mouth provides an alternative route over an oral drug administration for systemic as well as local drug delivery. The aim of the present study was to develop buccal tablet of Nefopam HCl to maintain constant therapeutic levels of the drug for over 10 hrs. Various grades of HPMC were employed as polymers. Nefopam HCl dose was fixed as 120 mg. Total weight of the tablet was considered as 500 mg. Polymers were used in the concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F2) showed better and desired drug release pattern i.e., 98.56% in 10 hours. It followed zero order release kinetics mechanism. As the buccal mucosa has an abundant blood supply and is relatively permeable, it can be considered as most accessible and desired location for both local and systemic drug delivery for the buccal cavity or bucco-adhesive systems.

KEYWORDS: Nefopam HCl, HPMC, Buccal Tablets, bucco-adhesive systems.

INTRODUCTION

For a prolonged duration of time two materials made to attach with one another by their interfacial forces and this phenomenon is known as bioadhesion.[1] If attachment is with

mucus layer then it is called mucoadhesion.[1,2] These mucoadhesive drug delivery systems uses bioadhesion property of certain polymers which on hydration become adhesive, therefore it is used as targeted drug for specific area of the body for prolonged duration of time.[3]

The classifications of mucoadhesive delivery system on the basis of route of application[4]

1. Ocular drug delivery system.
2. Buccal drug delivery system.
3. Gastro-intestinal drug delivery system.
4. Nasal drug delivery system.
5. Vaginal drug delivery system and.
6. Rectal drug delivery system.

Within the oral mucosal cavity, delivery of drugs is classified into three categories.[5]

1) Sublingual delivery: which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth 2) Buccal delivery: which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and 3) Local delivery: which is drug delivery into the oral cavity.

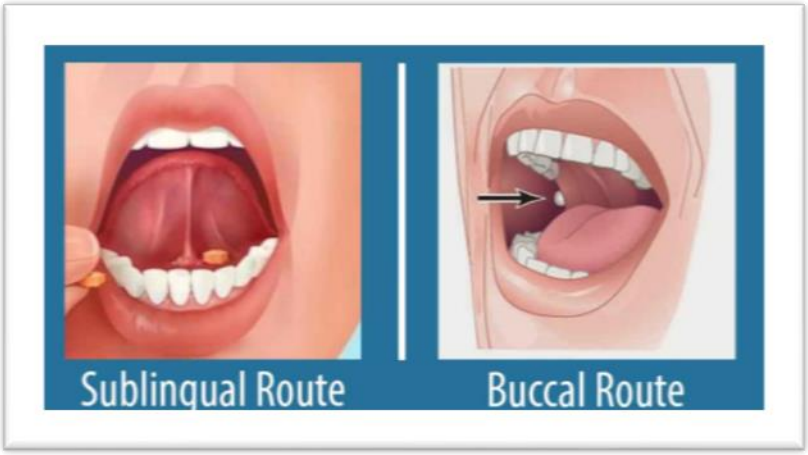

Fig 1: Sublingual Buccal Routes.

Advantages of bucco-adhesive drug delivery system.[6]

1. Avoids first pass metabolism and hence offers greater bioavailability.
2. Allows drug localization for a prolonged period of time.
3. Provides convenience for administration and termination of therapy in case of emergency.
4. Can be easily administered to unconscious patient.

5. It is possible to obtain significant dose decrease.
6. Drugs that are likely to be unstable in acidic or in an alkaline condition of stomach and intestine or drug that are susceptible to enzymatic degradation can be administered.
7. Drug absorption take place by passive diffusion.
8. Better patient compliance or acceptance.
9. Provides sustained delivery of drug.
10. Rapid onset of action.

Limitations of bucco-adhesive drug delivery system.[7]

1. Drugs that irritate oral mucosa, have odor and bitter taste, are unpalatable cannot be administered.
2. Drugs that are unstable at buccal pH cannot be administered.
3. Drugs with a low dosage need can be given.
4. Excess salivation may cause swallowing of drug.
5. Drugs that are absorbed through passive diffusion can be administered.
6. Food and liquid consumption may not be convenient.
7. Accidental swallowing of formulation by patients is possible.

Anatomy of the buccal mucosa: The oral mucosa has three distinctive layers namely the epithelium, connective tissue and basement membrane.[8] The stratified squamous epithelium coated with mucus is found on the outermost layer of oral mucosa. The thickness of epithelium is about 40-50 cell layers thick.[9]

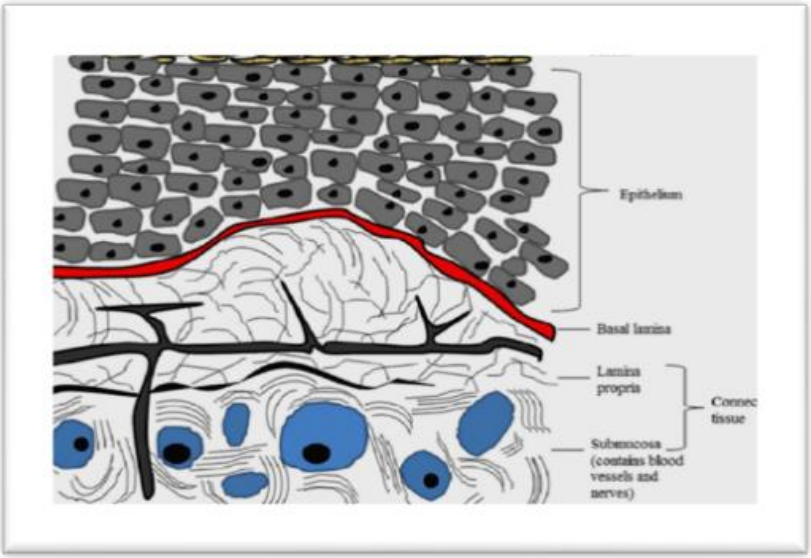

Fig 2: Structure of Buccal Mucosa.[5]

The oral mucosa consists of an exterior sheath known as stratified squamous epithelium and lamina propria backed up by the sub-mucosa as an innermost sheath. There are several sensory receptors consisting of tongue taste receptors. Buccal cavity membrane is classified into masticatory, lining as well as specialized mucosa. Masticatory mucosa consists of keratinized tissues, while lining mucosa consist of non-keratinized tissues lining the floor of mouth, lips and cheeks etc. In the oral cavity, different thickness and varied composition of non-keratinized and keratinized tissues are present, whereas mouth surface area is 50% composed of keratinized tissue and 30% is inhabited by non-keratinized tissues.[10]

Epithelium of buccal mucosa is not keratinized, consisting of squamous stratified epithelium. Lamina propria is a connective tissue overlie with several cell layers. Connective tissue layer is differentiated from epithelium by basement membrane. Tonofilament as huge amount of protein is present in most of the layers.[11]

According to five major regions in the oral cavity, oral mucosa can be distinguished into.[12,13]

The sublingual mucosa (mouth)

The buccal mucosa (cheeks)

The ginigiva (gum)

The palatal mucosa

The inner side of the lips

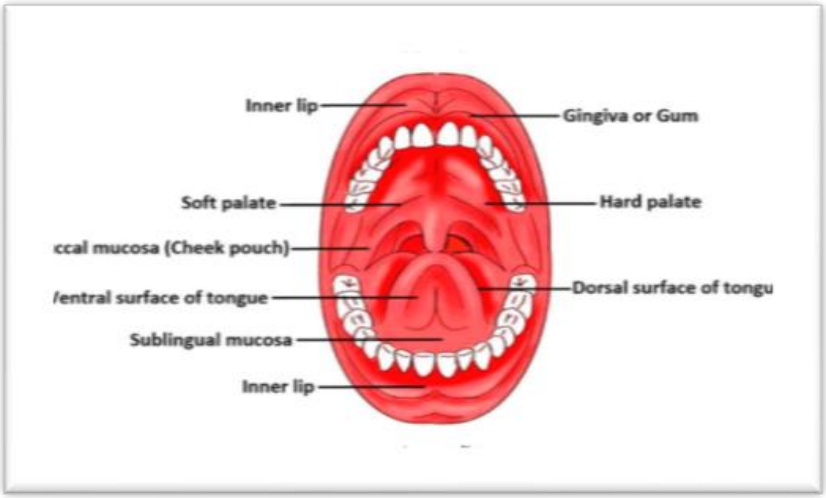

Fig 3: Oral Mucosa.

MATERIALS AND METHODS

Nefopam HCl was obtained as a gift sample from Natco labs Hyderabad, Telangana and

other chemicals & reagents were of SD fine chemicals provided by college.

METHODS OF PREPARATION: All the formulations were prepared by direct compression method. The preparation of different formulations includes various grades of HPMC, used for rate of release of the drug from the tablets. Magnesium stearate and talc as lubricant and glidant. Micro crystalline cellulose (MCC) added as binding agent. Lactose was included in formulation as hydrophilic agent. In all the formulations designed weight of a single tablet was kept constant, in table 1. The weight of a single tablet was 750mg.

Table 1: Formulations.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nefopam HCl	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg
HPMC K4M	120 mg	150 mg	200 mg	-	-	-	-	-	-
HPMC K15M	-	-	-	120 mg	150 mg	200 mg	-	-	-
HPMC K100M	-	-	-	-	-	-	120 mg	150 mg	200 mg
Lactose	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
Mg Stearate	60 mg	50 mg	40 mg	60 mg	50 mg	40 mg	60 mg	50 mg	40 mg
Talc	60 mg	50 mg	30 mg	60 mg	50 mg	30 mg	60 mg	50 mg	30 mg
MCC	60 mg	50 mg	30 mg	60 mg	50 mg	30 mg	60 mg	50 mg	30 mg
Total weight	**500 mg**	**500 mg**	**500 mg**	**500 mg**	**500 mg**	**500 mg**	**500 mg**	**500 mg**	**500 mg**

RESULTS AND DISCUSSION

Pre-Compressional Parameters

The characteristics of powders are most important to formulation. These basic properties of the powders have been utilized to develop the manufacture of many successful pharmaceutical dosage forms. Table 2 shows the powder blend properties of Nefopam HCl tablets.

Bulk density depends on particle size, shape and tendency of particles to adhere together, may influence compressibility, porosity, dissolution and other properties. The bulk density and tapped density of powder blend was found between 0.49±0.04 to 0.58±0.04 gm/cm^3 and 0.52±0.03 to 0.67±0.02 gm/cm^3, which indicates good packing capacity of powder blend. For inter particulate cohesive property, Carr's index was evaluated with angle of repose measurements and studied for the effects of geometry of packing solids with bulk and tapped density. Values of Carr's index below 15% usually show good flow characteristics and above 25% indicate poor flow ability. Carr's index was found to be between 16.21±0.06 to 17.97±0.02. Hausner's ratio method used to evaluate stability of powder column and to estimate the flow properties, it was found between 0.64±0.03 to 1.17±0.02. Low range

observed of Hausner's ratio which indicates good flow ability. The angle of repose of all the formulations were found to be within the range of 24.22 ± 0.15 to 25.67 ± 0.07 which showed that, granules were of good flow properties.

Table 2: Pre-Compressional Parameters Of All The Formulations.

Formulations	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index	Hausner Ratio	Angle of repose (θ)
F1	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06	25.11 ± 0.05
F2	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05	25.67 ± 0.07
F3	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03	25.54 ± 0.12
F4	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04	25.43 ± 0.10
F5	0.52±0.03	0.57±0.03	16.92±0.04	1.20±0.08	25.34 ± 0.04
F6	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09	24.22 ± 0.15
F7	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03	25.18 ± 0.02
F8	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09	24.23 ± 0.20
F9	0.55±0.08	0.52±0.03	17.54±0.09	1.17±0.02	25.05 ± 0.08

Evaluation of Post Compressional Parameters of Tablet Characteristics[14]

Nefopam HCl tablets were prepared by direct compression method and were evaluated for average weight, thickness, hardness, friability and drug content.

Tablet thickness, diameter and hardness

All the formulations were evaluated for various parameters like thickness; diameter and hardness. All the prepared tablets formulations F1 to F9 shown in Table 3, it was found that there was no much variation in thickness of tablets. Thickness and diameter of tablets of all formulations were measured by vernier caliper and there will be no any change in thickness and diameter of tablets respectively. Thickness was in range of 2.2 ± 0.01 to 2.6 ± 0.03. The hardness of tablets was measured by Pfizer hardness tester. The hardness was in range of 4.4 to 4.9 Kg/cm^2.

Weight Variation

The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation. The results are showed in table 3.

Friability

The present study of tablets is within the limit and the slight variation in seen in friability because of the variation in compression force applied and its total weight. The friability of

tablets also depends on type of filler and moisture contents present in it. The friability was found in the range of 0.42 ± 0.067 to 0.60 ± 0.034 shown in Table 3.

Drug Content

The drug content studies were carried out for all the prepared formulations and it was in range of 98.34 ± 0.18 to 99.76 ± 0.20, which reflects good drug content uniformity in all the prepared formulations. The reading complies as per I.P. which indicates drug was uniformly distributed throughout the tablet compressed. The results are shown in Table 3.

Table 3: Post-Compressional Properties Of Prepared Tablets.

Formulations	Average Weight (Mg)	Thickness (Mm)	Diameter (Mm)	Hardness (Kg/Cm^2)	Friability (%)	Drug Content (%)
F1	502 ± 0.03	2.2 ± 0.01	11.8 ± 0.02	4.7± 0.08	0.48 ± 0.033	99.45 ± 0.17
F2	501 ± 0.03	2.2 ± 0.03	11.9 ± 0.03	4.6 ± 0.03	0.43 ± 0.023	99.34 ± 0.19
F3	449 ± 0.03	2.3 ± 0.01	11.7 ± 0.07	4.4 ± 0.01	0.42 ± 0.067	99.65 ± 0.23
F4	501 ± 0.03	2.2 ± 0.04	12.9 ± 0.01	4.8 ± 0.02	0.45 ± 0.066	99.76 ± 0.20
F5	509 ± 0.03	2.6 ± 0.03	12.8 ± 0.04	4.7 ± 0.02	0.60 ± 0.034	99.42 ± 0.16
F6	448 ± 0.06	2.3 ± 0.04	12.6 ± 0.02	4.5 ± 0.03	0.52 ± 0.078	98.34 ± 0.18
F7	504 ± 0.03	2.5 ± 0.05	12.4 ± 0.03	4.4 ± 0.06	0.54 ± 0.032	98.54 ± 0.22
F8	507 ± 0.03	2.3 ± 0.01	12.7 ± 0.09	4.9 ± 0.04	0.52 ± 0.010	99.62 ± 0.18
F9	505 ± 0.03	2.4 ± 0.03	12.3 ± 0.08	4.6 ± 0.02	0.53 ± 0.077	99.13 ± 0.12

***Invitro* Dissolution Study**

Study was conducted for 10 hours by using pH 6.8 phosphate buffer as dissolution medium, all the formulations showed good drug release rate, whereas formulation F2 showed 98.56±0.92% drug release at 10 hours. Results are in table 4, 5 & 6 and release data in figure 4, 5 & 6. Depending upon the release data F2 formulation was considered as promising formulations among all.

Table 4: In-Vitro Release Study Of Nefopam Hcl Tablets: F1 To F3.

Timings	F1	F2	F3
0 hr	0	0	0
1 hr	10.45 ± 0.12	10.45 ± 0.22	14.56 ± 0.19
2 hr	20.46 ± 0.18	21.78 ± 0.11	21.67 ± 0.10
3 hr	32.65 ± 0.21	27.76 ± 0.13	34.62 ± 0.21
4 hr	48.71 ± 0.11	38.76 ± 0.19	48.43 ± 0.14
5 hr	56.62 ± 0.10	45.87 ± 0.16	58.92 ± 0.12
6 hr	69.35 ± 0.20	55.63 ± 0.10	63.43 ± 0.16
7 hr	77.51 ± 0.22	69.43 ± 0.19	77.13 ± 0.13
8 hr	81.54 ± 0.10	79.56 ± 0.17	85.34 ± 0.11
9 hr	87.82 ± 0.14	88.67 ± 0.82	88.42 ± 0.19
10 hr	90.13 ± 0.09	98.56 ± 0.92	92.18 ±0.78

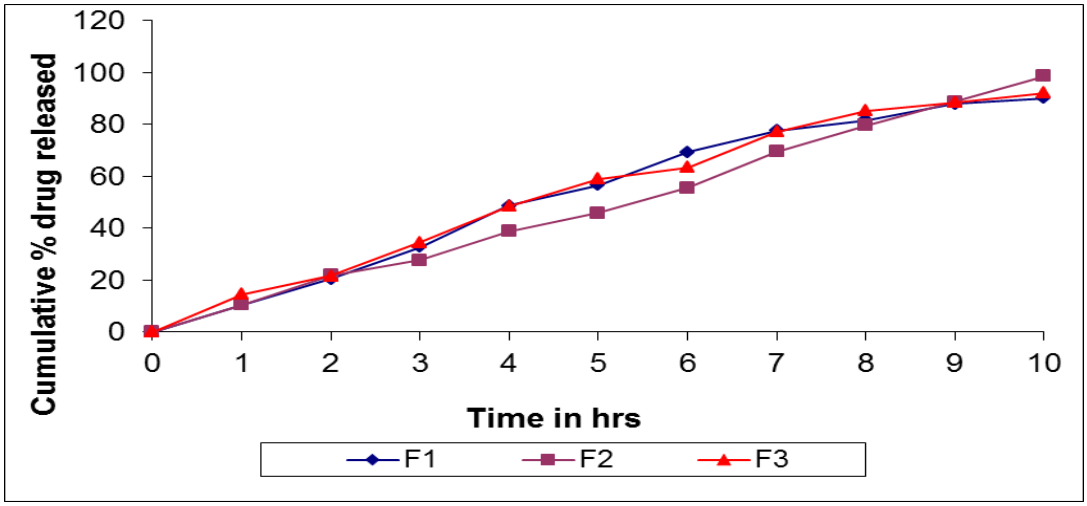

Fig 4: in-vitro release study of nefopam hcl tablets: f1 to f3.

Table 5: In-Vitro Release Study Of Nefopam Hcl Tablets: F4 To F6.

Timings	F4	F5	F6
0 hr	0	0	0
1 hr	10.54 ± 0.18	11.56 ± 0.43	13.65 ± 0.22
2 hr	21.56 ± 0.19	25.75 ± 0.32	19.78 ± 0.62
3 hr	29.87 ± 0.11	37.74 ± 0.22	28..18 ± 0.92
4 hr	39.1 ± 0.19	49.54 ± 0.33	38.89 ± 0.67
5 hr	44.98 ± 0.24	56.27 ± 0.30	48.67 ± 0.90
6 hr	56.92 ± 0.54	66.75 ± 0.87	59.91 ± 0.42
7 hr	68.77 ± 0.66	79.63 ± 0.41	69.41 ± 0.21
8 hr	77.65 ± 0.32	85.75 ± 0.40	76.98 ± 0.88
9 hr	88.56 ± 0.45	90.17 ± 0.57	81.65 ± 0.32
10 hr	93.19 ± 0.76	91.32 ± 0.35	89.71 ± 0.65

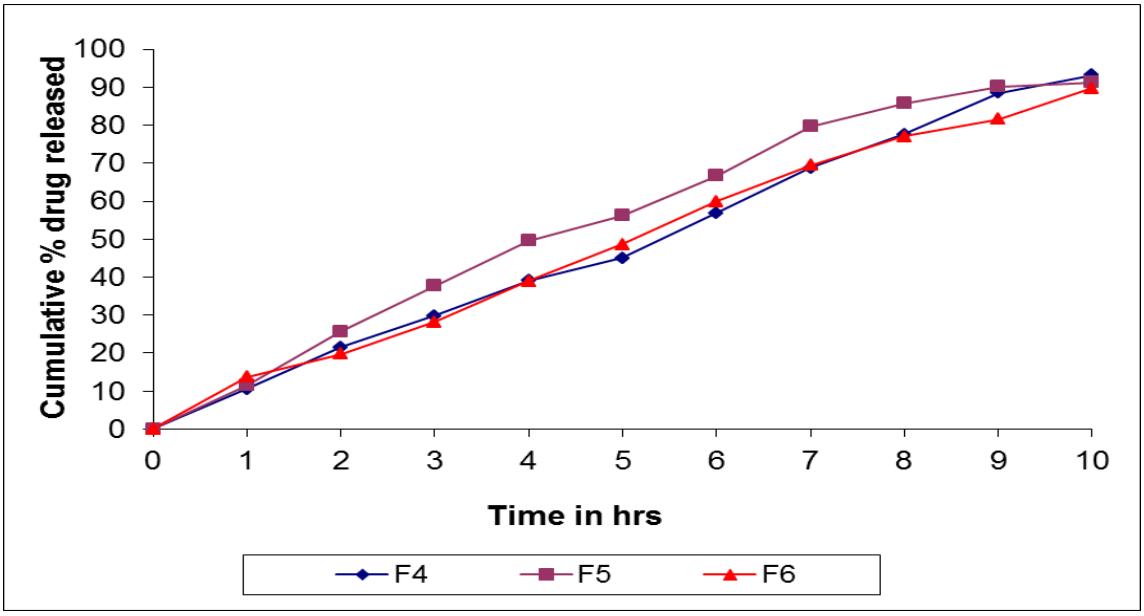

Fig 5: In-Vitro Release Study of Nefopam Hcl Tablets: F4 To F6.

Table 6: **In-Vitro Release Study of Nefopam Hcl Tablets: F7 To F9.**

Timings	F7	F8	F9
0 hr	0	0	0
1 hr	9.31 ± 0.22	11.71 ± 0.32	10.53 ± 0.72
2 hr	15.67 ± 0.62	21.65 ± 0.41	32.53 ± 0.14
3 hr	22.78 ± 0.36	38.76 ± 052	45.71 ± 0.34
4 hr	34.76 ± 0.77	49.71 ±0.50	52.56 ± 0.90
5 hr	43.78 ± 0.89	57.41 ± 0.72	63.43 ± 0.52
6 hr	55.76 ± 0.66	65.81 ± 0.81	72.31 ± 0.31
7 hr	62.87 ± 0.21	72.76 ± 0.92	80.31 ± 0.88
8 hr	75.61 ± 0.92	77.61 ± 0.31	83.67 ± 0.67
9 hr	81.76 ± 0.45	85.45 ± 0.22	88.91 ± 0.27
10 hr	89.94 ± 0.32	90.16 ± 0.92	90.31 ± 0.35

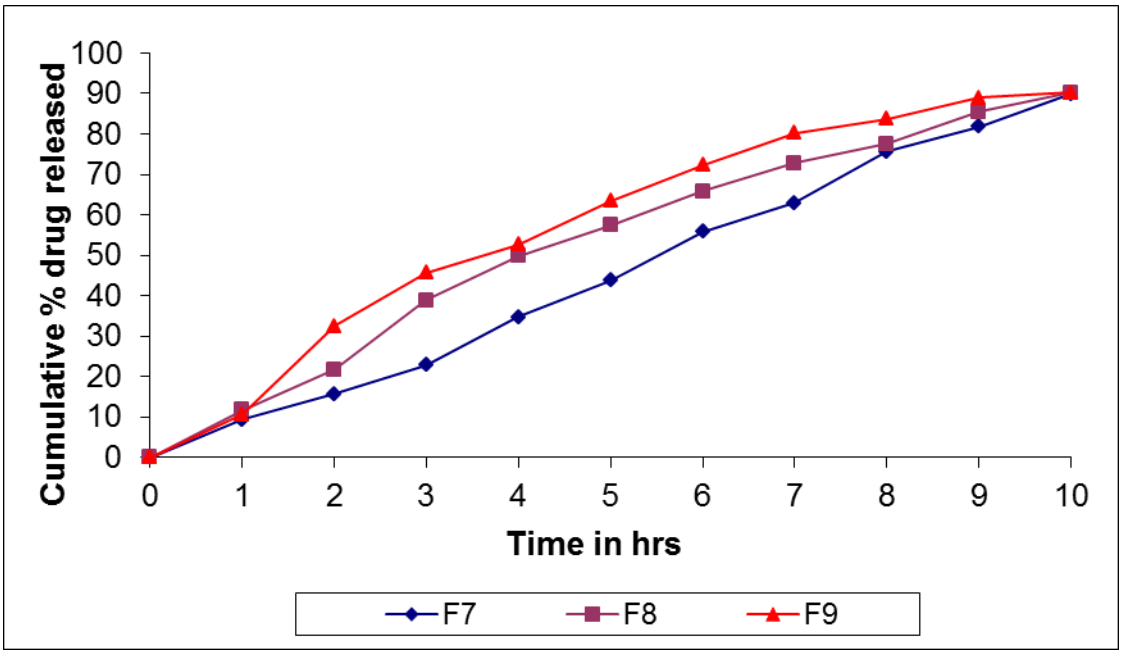

Fig 6: **In-Vitro Release Study of Nefopam Hcl Tablets: F7 To F9.**

STABILITY STUDIES

The most promised formulations were selected stability studies. Three month stability studies were performed as per ICH guidelines at a temperature of $45^0 \pm 1^0$ C over a period of three month on the promising Floating tablet formulation F2. Sufficient number of tablets (10) were packed in aluminium packing and kept in stability chamber maintained at $45^0 \pm 1^0$ C / 75 ± 5 % RH for 3 months. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and *in-vitro* studies were performed to determine the drug release profiles, the estimation of drug contents and data of dissolution and *in-vitro* studies are shown in table 7 and *in-vitro* release data of the stability in Figure 7.

Table 7: Stability Studies of Formulation F2.

Sl. No.	Time in days	Physical changes	Mean ± SD (45±1°C)
1.	01	--	98.56±0.91
2.	30	No Change	99.78±1.20
3.	60	No Change	96.12±1.02
4.	90	No Change	99.23±0.67

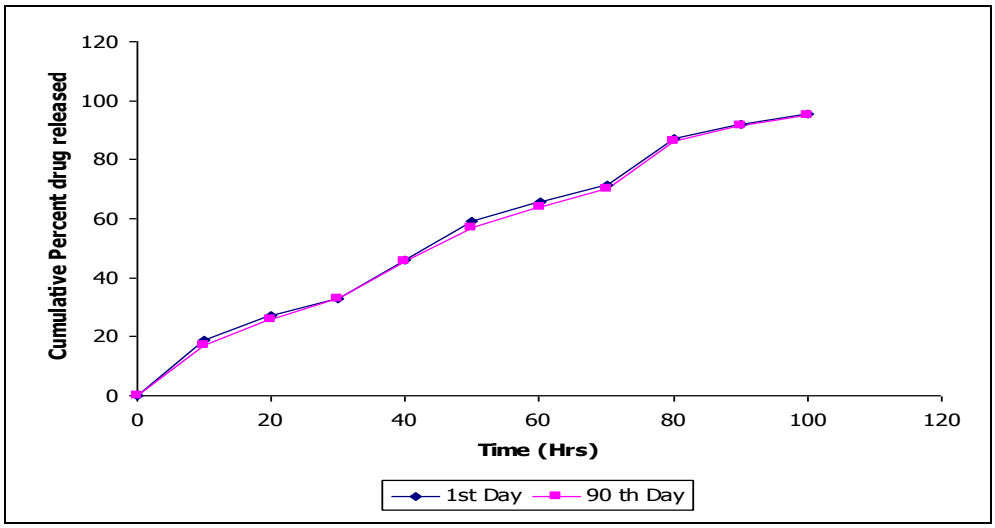

Fig 7: Stability Studies of Formulation F7.

FTIR Studies: Compatibility of drug-polymer studies were conducted using FTIR spectrophotometer by KBr pellet technique of pure drug and best formulation was determined. FTIR spectra are in Figure 8 & 9 respectively.

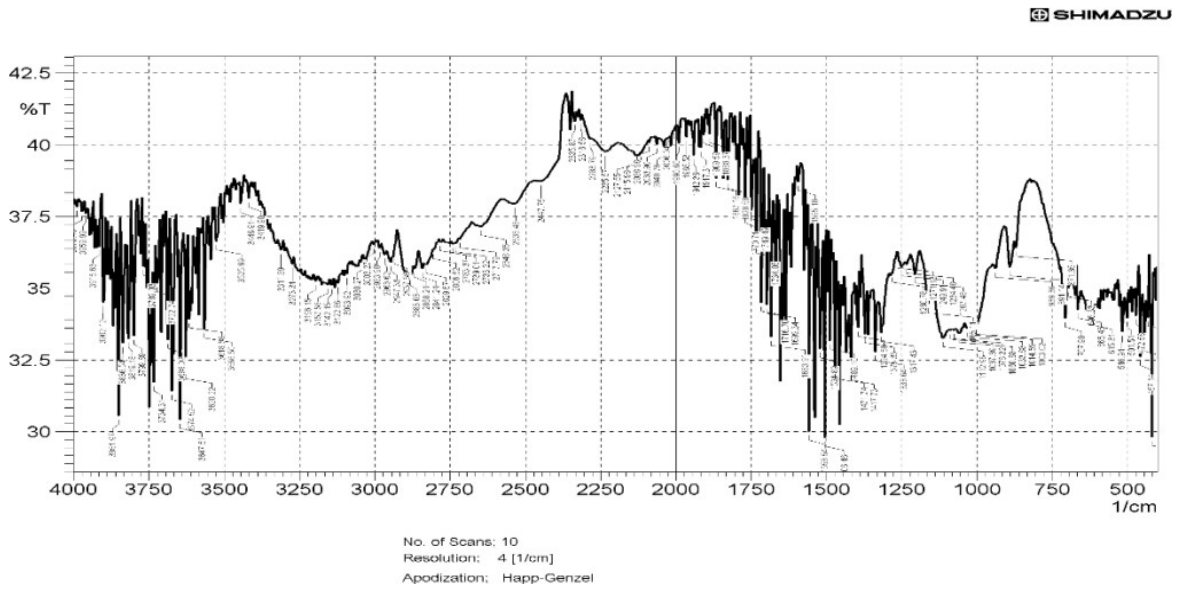

Fig 8: Ftir Spectrum Of Pure Drug.

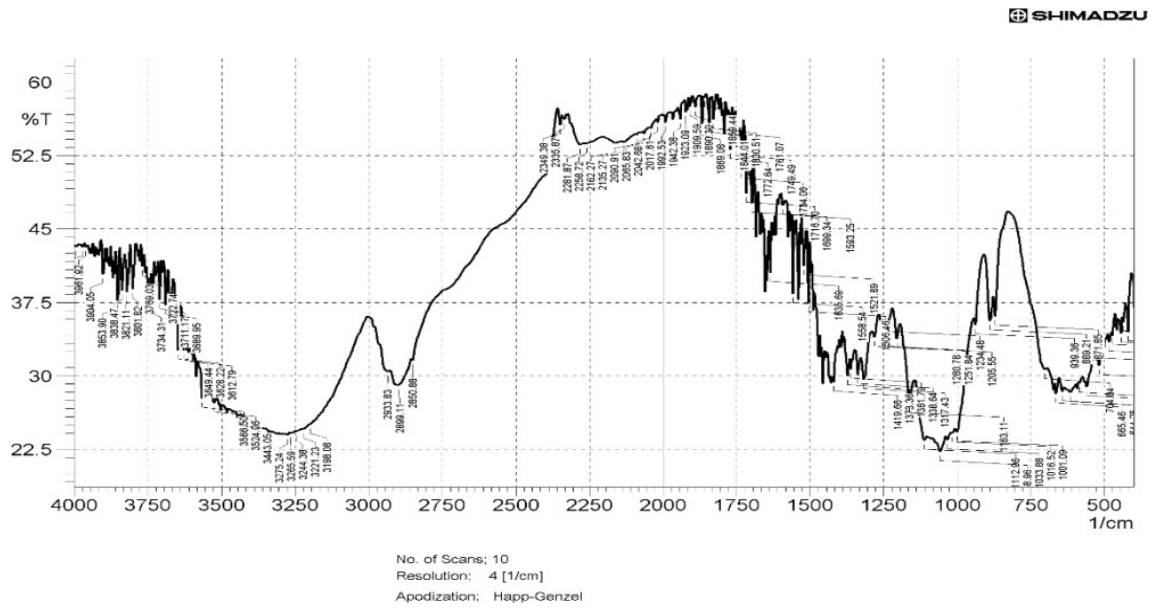

Fig 9: Ftir Spectrum of Optimised Formulation F2.

CONCLUSION

The study was to develop buccal formulation of Nefopam HCl to maintain constant therapeutic levels of the drug for over 10 hrs. Various grades of HPMC were employed as polymers. Nefopam HCl dose was fixed as 120 mg. Total weight of the tablet was 500 mg. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F2) showed better and desired drug release pattern i.e., 98.56 % in 10 hours. It followed zero order release kinetics mechanism.

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