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Article

DEVELOPMENT, *IN-VITRO AND EX-VIVO* EVALUATION OF MUCO-ADHESIVE BUCCAL TABLETS OF HYDRALAZINE HYDROCHLORIDE

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Hydralazine hydrochloride is an anti-hypertensive drug. The drug has poor oral bioavailability (BA) of about 30- 50% due to extensive first-pass metabolism. Hence, the buccal delivery was used to enhance the BA of hydralazine hydrochloride. Buccal muco-adhesive tablets were prepared by direct compression technique, using carbopol 934P, HPMC K_4M, sodium alginate and sodium carboxy methyl cellulose (NaCMC) as muco-adhesive polymers. Prepared formulations were evaluated for physico-chemical characterization, *ex-vivo* residence time and *in-vitro* release studies. The some of the parameters viz hardness, thickness, weight variation are showing the values within the pharmacopeial limits. However, the swelling and bio-adhesive strength were increased with increasing polymer concentrations. From the *in-vitro* release studies, F9 buccal tablets prepared with NaCMC exhibited better release (96.56%, 6 h) profile than all other formulations and considerd as optimized. The release mechanism from kinetic methods suggests that, the drug release follows zero-order kinetics with diffusion mechanism. Thus, the buccal tablets of hydralazine hydrochloride showed enhanced BA and were further confirmed by *in-vivo* studies.

Key Words: Hydralazine hydrochloride. First-pass metabolism. Buccal muco-adhesive tablets. *In-vitro, ex-vivo.*

INTRODUCTION

Oral route is most preferred and widely applicable route for the delivery of majority of the drugs. But the problems such as poor aqueous solubility, less residence time, chemical instability in the gastrointestinal tract minimize the bioavailability (BA) of orally administered drugs (Dudhipala, Veerabrahma, 2016**)**. Further, metabolism through various barriers or enzymes also degrades the drug before reaching site of action. Hence, various alternative drug delivery systems are developed to enhance the oral BA of these drugs. The delivery systems include; enhancement of solubility through solid dispersions (Ettireeddy *et al.,* 2017), complexation with cyclodextrins (Palem *et al.,* 2016a), liquisolid compacts (Arun *et al.,* 2018), increase the stability and prolonged residence time through floating systems (Dudhipala *et al*., 2011; Senjoti *et al*., 2016; Dudhipala *et al.,* 2016), increase the mucoadhesive property (Bomma *et al.,* 2014); lipid based delivery systems for by passing metabolism with solid lipid nanaoparticles (Dudhipala, Veerabrahma, 2015), transfersomes (Pitta *et al.,* 2018), nanostructured lipid carriers (Dudhipala *et al.,* 2018**)** and micronization for reducing particle size using nanosuspensions (Nagaraj *et al*., 2017; Butreddy *et al.,* 2015).

The oral cavity is easily accessible for self-medication and is well accepted by patients. In the last three decades, there is a great interest in the research of buccal drug delivery system (Senel, Hincal, 2001). The

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oral cavity is the most attractive route for drug delivery due to its ease of administration. Both locally acting and systemic acting drugs can be administered by this route. The site-specific release of drug at mucosa is achieved when used for local activity and systemic action requires drug absorption through the mucosal barrier to reach systemic circulation (Palem *et al.,* 2011a).

Several approaches have been investigated to improve absorption through buccal mucosa by addition of permeation enhancers is one of the approaches. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Incorporation of permeation enhancers improves the delivery of drug via buccal membrane, which could reduce barrier properties of the buccal epithelium (Schipper *et al.,* 1997). Compared to the intestinal, rectal and nasal mucosa, oral mucosa is highly vascularized with reduced enzyme activity, less sensitive to damage and irritation. The oral mucosa consists of sublingual mucosa and buccal mucosa for delivery of drugs with high permeability for acute diseases and prolonged for chronic diseases respectively (Kumar *et al.,* 2014). For oral mucosal drug delivery system, the mucosa consists of great surface area which is usually rich in blood supply. To provides for rapid drug transport to the systemic circulation through the internal jugular bypasses drugs from the hepatic first-pass metabolism, avoiding drug degradation in acidic stomach environment and enhances drug bioavailability (Rojanasakul *et al.,* 1992; Zhang *et al.,* 2002; Harris, Robinson, 1992; Palem *et al.,* 2016b; Jaipal *et al.,* 2016).

Hydralazine hydrochloride is used widely for treating hypertension. The drug is well absorbed from the gastrointestinal tract but its bioavailability is low (30- 50%) due to extensive first pass metabolism. Since the buccal route bypasses the first-pass metabolism, the dose of hydralazine hydrochloride could be reduced by 50%. The physicochemical properties of hydralazine hydrochloride, its suitable half-life (3-7 h) and low molecular weight (196.64) and smaller dose and absence of objectionable taste and odour make it suitable candidate for buccal administration (Mary *et al.,* 2000; Palem *et al*., 2015).

MATERIAL AND METHODS

Hydralazine hydrochloride was obtained as a gift sample from Stride's lab, Bangalore India. Carbopol 934P was obtained from S.D. Fine Chemicals, Mumbai. Hydroxy propyl methyl cellulose (HPMC K4M) and sodium carboxy methyl cellulose (Na-CMC) was obtained from Loba chemicals, Mumbai. Micro crystalline cellulose (MCC) obtained from Laksmi chemicals, India PEG 6000 obtained from India glycol Pvt Ltd., Mumbai, India. All other ingredients used in formulations were of analytical grade.

Preparation of hydralazine hydrochloride muco-adhesive buccal tablets

Buccal muco-adhesive tablets were prepared by direct compression technique using variable concentration of carbopol 934P, HPMC K4M and sodium carboxy methyl cellulose (Na-CMC). The drug, respective polymer and MCC have weighed accurately and then passed through sieve No.100 to get uniform particle size. Then all the ingredients except lubricants and glidants were mixed by triturating for 10 to 15 min in a mortar with a pestle to obtain a uniform mixture. Finally, magnesium stearate and talc were added. The blended powder was compressed into tablets weighing 150 mg using a tablet machine having a flat-faced punch and die set of 8 mm diameter ((Rimek Minipress Karnavati Engg. Ltd, Ahmadabad, India). All the formulations are containing 25 mg of hydralazine hydrochloride and combination of carbopol 934P with HPMC K_4M and NaCMC polymers in different ratios. The formulations are shown in Table I.

TABLE I - Formulation of muco-adhesive buccal tablets of Hydralazine hydrochloride

Formulation	Carbopol 934P	HPMC K4M	Na CMC	MCC	Mg Stearate	Talc
F1	30	30	-	61	2	2
F2	20	40	-	61	2	2
F3	40	20	-	61	2	2
F4	15	45	-	61	2	2
F5	45	15	-	61	2	2
F6	30	-	30	61	2	2
F7	20	-	40	61	2	2
F8	40	-	20	61	2	2
F9	15	-	45	61	2	2
F10	45	-	15	61	2	2

Evaluation of muco-adhesive buccal tablets

Determination of weight variation: This is an important quality control test to be checked for any variation in the weight of tablets that leads to either under or overdose. So every batch should have a uniform weight (USP, 1990).

Method: Twenty tablets were randomly selected from each formulation and their average weight and standard deviation were calculated from the total weight of all tablets. The % difference in the weight variation should be within the permissible limits. The % deviation was calculated. The limits are mentioned in the below Table II as per USP.

TABLE II - Maximum % deviation allowed for weight variation of tablets

Average weight of the tablets (mg)	Maximum % difference allowed
130 or less	±10
130-324	±7.5
More than 324	±5

Thickness

The thickness of buccal tablets was determined with the help of Vernier calipers. Three individual tablets from each formulation were used and the results averaged.

Hardness

Hardness is an important quality control test to be indicated for measuring the ability of a tablet to withstand mechanical shocks while handling. The test was conducted for 3 tablets from each formulation using Monsanto hardness tester; the average and standard deviation values were calculated (Lachman, 2009).

Friability

It is a measure of mechanical strength of tablets. Roche friabilator was used to determine the friability by the following procedure. Pre-weighed tablets (10 tablets) were placed in the friabilator. This device consists of a plastic chamber that is set to revolve around 100 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. At the end of the test, tablets were reweighed; loss in the weight of the tablet is the measure of friability and is expressed in percentage as:

$$F\ (\%) = [1-W_F/Wo]x100$$

Where, Wo is the weight of the tablets before the test and W_F is the weight of the tablets after test

Drug content

Ten tablets were weighed and grounded in a mortar with a pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in phosphate buffer pH 6.8 for 10 minutes, added sufficient buffer and filtered through filter paper, 1ml of filtrate was suitably diluted with buffer and drug content was analyzed spectrophotometrically at 260nm using a UV spectrophotometer (IP, 1996).

Swelling studies of buccal tablets

Appropriate swelling behavior of a buccal adhesive system is an essential property for uniform and effective muco-adhesion (Kashappa, Pramod, 2004). Swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. The swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug and bio-adhesiveness. The agar plate model used in this study resembles the secreting fluid around the buccal mucosa (Emami, Varshosaz, Saljoughian, 2008). For each formulation, three buccal tablets were weighed individually (W_1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 1 ºC. After every 1 hr time interval until 6 hr, the tablet was removed from the petri-dish and excess surface water was removed carefully with blotting paper. The swollen tablet was then reweighed (W_2) and the swelling index (SI) was calculated using the following formula (Patel *et al*., 2007; Perioli *et al.,* 2007; Palem *et al*., 2011b).

$$\text{Swelling Index} = [(W_2-W_1) \div W_1] \times 100$$

Where,

W_1 = initial weight of the tablet

W_2 = final weight of the swollen tablet

Ex-vivo Muco-adhesion Strength

Muco-adhesion may be defined as the adhesion between a polymer and mucus. In general, muco-adhesion is considered to occur in 3 major stages; wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of muco-adhesion is affected by various factors such as molecular weight of the polymers, contact time with mucus, swelling rate of the polymer and biological membranes used in the study (Perioli *et al.,* 2007).

The muco-adhesive strength of the buccal tablets was measured by the Modified Physical Balance which is shown in Figure 1. In this method porcine buccal membrane as the model mucosal membrane. The fresh porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. The both pans were balanced by adding an appropriate weight on the left- hand pan. A piece of the mucosa was tied to the surface of the beaker and placed below the right pan which was moistened with phosphate buffer pH 6.8. The tablet was sticky to the lower side of right pan with glue. Previously weighed beaker was placed on the left-hand pan and water (equivalent to weight) was added slowly to it until the tablet detaches from the mucosal surface. The weight required to detach

the tablet from the mucosal surface gave the muco-adhesive strength. The experiment was performed in triplicate and the average value was calculated (Park, Robinson, 1987).

Force of adhesion (N) = (muco-adhesive strength/100) ×9.8

Bond strength (N/m^2) = Force of adhesion (N) / Surface area of tablet (m^2)

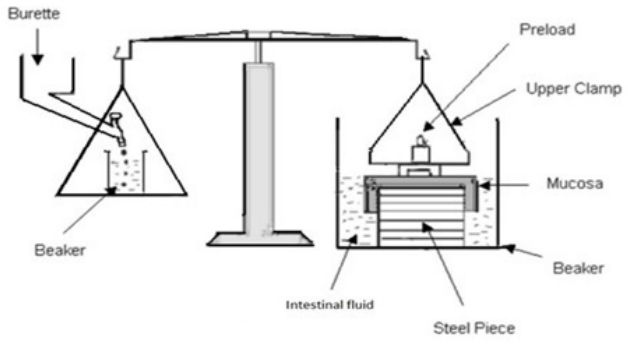

FIGURE 1 - Muco-adhesive strength measurement device.

Determination of the *ex-vivo* residence time

The *ex-vivo* residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 500 mL pH 6.8 phosphate buffer maintained at 37^0C. The porcine buccal tissue was glued to the surface of a glass slab, vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5 ml of pH 6.8 phosphate buffer and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to run test. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded. The experiments were performed in triplicate and mean was determined (Ramana, Nagada, Himaja 2007).

In-vitro drug release studies

USP type II rotating paddle method was used to study the drug release from the tablet. The dissolution medium consisted of 500 ml phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5 ºC, with a rotation speed of 50 rpm. The backing layer of the buccal tablet was attached to the glass slide with cyanoacrylate adhesive. The glass slide was placed at the bottom of the dissolution vessel. Samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by UV visible spectrophotometer (Elico SL 159) at 260nm. Released drug content was determined from calibration curve. All dissolution studies were performed in triplicate and mean was determined (Asha *et al.,* 2010; Chandira *et al.,* 2009; Nakath *et al.,* 2007).

Ex-vivo drug permeation study of buccal tablets

The porcine buccal mucosa was collected from the local slaughter house and was immediately transported to the laboratory in cold normal saline solution. The buccal mucosa was carefully separated from fat and muscles using a small sharp blade. The buccal mucosal epithelium was used within two hours. The *in-vitro* buccal drug permeation study was performed using a Franz diffusion cell at 37 ºC ± 0.5 ºC. The buccal mucosa was fixed between the donor and receptor compartments. The receiver chamber (50 ml capacity) was filled with phosphate buffer pH 6.8. The buccal mucosa was allowed to stabilize for a period of 30 min. The buccal tablet was placed in donor chamber and 1mL of buffer solution (pH 6.8) was added and the tablet was placed with the core facing the mucosa, and the compartments were clamped together. The hydrodynamics in the receiving compartment was maintained by continuous stirring with a magnetic bead at a uniform speed throughout the study (Brahmankar, Jaiswal, 2003; Satyabrata, Murthy, Padhy, 2010; Himabindu *et al.,* 2018). Samples were collected at predetermined time intervals. The amount of drug permeated through the buccal mucosa was then determined by UV spectrophotometer at 260 nm.

Release kinetics

Data of *in-vitro* release was fit into different equations to explain the release kinetics of drug from buccal tablets. The release data of buccal tablets was fitted into different mechanism models like zero order, first order, Higuchi, Korsemeyer - Peppas and Hixson – Crowell models to interpret the drug release mechanism from tablets.

a) *Zero-order release kinetics*

It defines a linear relationship between the fractions of drug released versus time

Q = kt
Where,
Q is the fraction of drug released at time t
K is the zero order release rate constant

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

b) *First order release kinetics:*

The equation used to describe first order release kinetics is

In (1-Q) = -kt
Where,
Q is the fraction of drug released at time t and
K is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of the drug remained against time will be linear if the release obeys first order release kinetics.

c) *Higuchi (Diffusion) equation*

A plot of the fraction of drug released against the square root of time will be linear if the release obeys Higuchi equation.

Q = kt1/2
Where,
Q is the fraction of drug released at time t
k is the release rate constant.

d) *Korsemeyer – Peppas kinetics*

A plot of the fraction of the logarithm of % drug released against the logarithm of time will be linear if the release obeys Korsemeyer – Peppas equation.

Log Q = log k + n log t
Where,
k is the release rate constant.

The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation (Peppas *et al*., 1985) shown in an equation.:

Mt/M∞ = ktn
Where,
Mt/M∞ is a fraction of drug released at time‘t’, k represents a constant, and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process.

Peppas (1985) used this n value in order to characterise different release mechanisms, for non-fickian release, the value of n falls between 0.5 and 1.0; while in the case of fickian diffusion,it is less than n = 0.5; For zero-order release (case II transport), n = 1; and for super case II transport, n > 1 (Agarwal, Mishra, 1999).

e) *Hixson-Crowel (Erosion) model*

This equation defines the drug release based on formulation erosion alone.

Q = 1-(1-kt)3
Where
Q is the fraction of drug released at time t
k is the release rate constant

Thus a plot between (1-Q)1/3 against time will be linear if the release obeys erosion equation (Jug, Becirevic-Lacan 2004; Rao *et al*., 2007; Costa, Lobo, 2001; Peppas, 1985, Higuchi, 1963).

FTIR studies to determine the drug excipient compatibility

Fourier Transform Infrared (FTIR) model analysis was performed to interpret the interactions of drug with polymers and other ingredients.

RESULTS AND DISCUSSION

Weight variation, Thickness, Hardness, Friability and Drug content

All the prepared tablets were subjected to various tests such as hardness, weight variation, thickness and drug content study as described in earlier sections.

The results of tests viz., hardness, weight variation, thickness, drug content were found be within the pharmacopeial limits. The results are shown in Table III.

TABLE III - The physical evaluation of muco-adhesive buccal tablets

Formulation	Weight variation† (mg)	Thickness* (mm)	Hardness* (kg/cm²)	Friability* (%)	Drug content*
F1	152.85	2.16±0.020	3.41±0.14	0.56±0.11	98.17±1.54
F2	150.60	2.16±0.020	3.36±0.26	0.65±0.13	97.35±2.31
F3	151.65	2.15±0.011	3.44±0.11	0.51±0.10	97.35±1.42
F4	150.35	2.15±0.015	3.44±0.16	0.53±0.07	98.45±1.03
F5	151.05	2.14±0.015	3.54±0.11	0.41±0.12	99.26±1.25
F6	152.25	2.16±0.015	3.41±0.20	0.58±0.11	98.93±1.51
F7	149.10	2.14±0.010	3.55±0.27	0.44±0.18	97.51±0.98
F8	151.95	2.14±0.011	3.53±0.10	0.46±0.16	98.33±1.38
F9	151.65	2.15±0.015	3.41±0.14	0.56±0.11	98.17±1.54
F10	149.33	2.14±0.015	3.54±0.13	0.51±0.12	99.15±1.25

†all the weight variation values of -3.323 to + 2.976%, *Each value represents the mean ± SD of 3.

Swelling studies of buccal tablets

The muco-adhesion and drug release profile are dependent upon swelling behavior of the tablets. The muco-adhesive polymers were hygroscopic and retain large amounts of water. From the results, it is clear as the swelling index increased as the time proceeds.

The swelling values of the tablets showed an increase in swelling value with an increase in polymer content. Formulation F3 given maximum swelling and was found to be 60% within 6 h. The plots of percentage swelling index are shown in Figure 2.

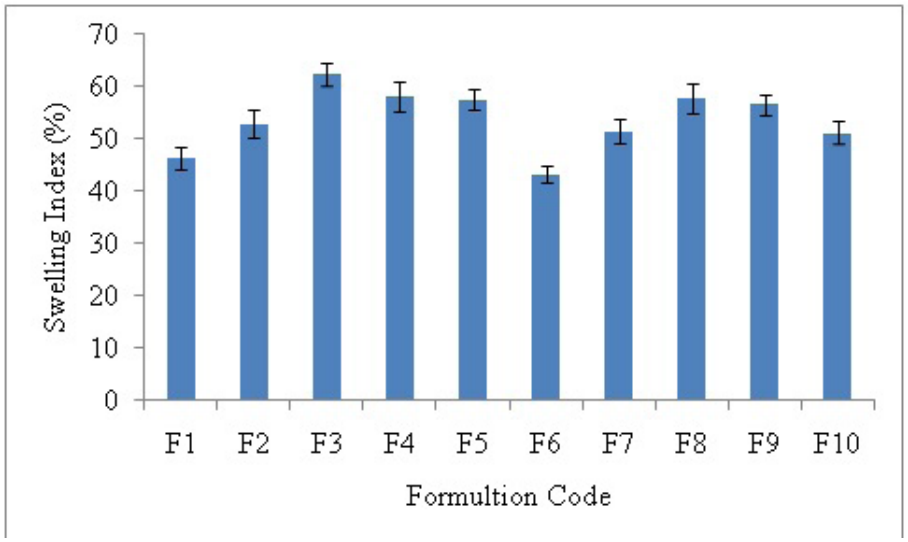

FIGURE 2 - Percentage of swelling of developed buccal tablets.

Ex-vivo muco-adhesion strength

The muco-adhesion property of hydralazine hydrochloride tablets was affected by the type and concentration of the muco-adhesive polymers. Hydralazine hydrochloride tablets containing carbopol 934P and HPMC K4M at the ratio of 2:1 (F3) exhibited highest muco-adhesive strength (39.33±3.36 N/m^2) with the buccal mucosa when compared with other formulations due to higher amount of carbopol 934P polymers.

However, optimized formulation F9 showed 36.43±3.08 good muco-adhesive strength (36.43±3.08) with porcine buccal mucosa due to swelling and contact time. The optimized formulation (F9) showed 36.43±3.08 gm of muco-adhesive strength (Table IV).

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TABLE IV - Muco-adhesive properties of prepared buccal tablets

Formulation	Muco-adhesive Strength*
F1	33.18±3.53
F2	34.58±2.52
F3	39.33±3.53
F4	35.52±3.53
F5	37.06±3.36
F6	28.82±2.53
F7	34.35±2.58
F8	37.28±3.53
F9	36.43±3.08
F10	37.25±3.66

*Each value represents the mean ± SD of 3

Determination of *ex-vivo* residence time

The *ex-vivo* residence time is one of the important physical parameters of buccal muco-adhesive tablets. The *ex-vivo* residence properties of the tablets were determined using porcine buccal mucosa. The results revealed that formulation containing carbopol 934P and HPMC K4M (F1-F5) showed higher muco-adhesive retention time when compared to the formulations containing carbopol 934P and Na CMC (F6-F10) as showed in Table V.

TABLE V - *Ex-vivo* residence time of buccal tablets

Formulation	*Ex-vivo* residence time (hr)
F1	5hr 30min
F2	5hr 20min
F3	5hr 50min
F4	5hr 10min
F5	> 6 hr
F6	5hr 20min
F7	5hr 10min
F8	5hr 35min
F9	5hr 15min
F10	5hr 30min

In-vitro drug release of buccal tablets

In-vitro release of hydralazine hydrochloride buccal tablets was performed in pH 6.8 phosphate buffer and the results are in Figure 3, 4 and 5. The *in-vitro* drug release profiles of hydralazine hydrochloride from buccal tablets, which is containing carbopol, HPMC K_4M and Na-CMC polymers in the ratio of 1:1, 1:2, 2:1, 1:3 and 3:1. The most important factor affecting the rate of drug release from the buccal tablets was the drug and polymers ratio. In all the formulations the drug release was ranging from 76.75% to 96.59%. In all the formulations, the release rate of hydralazine hydrochloride decreased with increasing concentration of carbopol 934P, HPMC K4 M and Na-CMC. This could be due to the increase in the viscosity of the gel as well as the formation of a gel layer.

From the results, formulation F9 exhibited better release (96.59±1.69) in 6th hour, which may be due to the hydrophilicity, water uptake, which creates a water-swollen gel-like state that sustaining the release of drug with satisfactorily controlled manner. It is evident from the results shown in figure 4 below, the formulation F9 is showing controlled release profile which may be due to increased diffusion pathway.

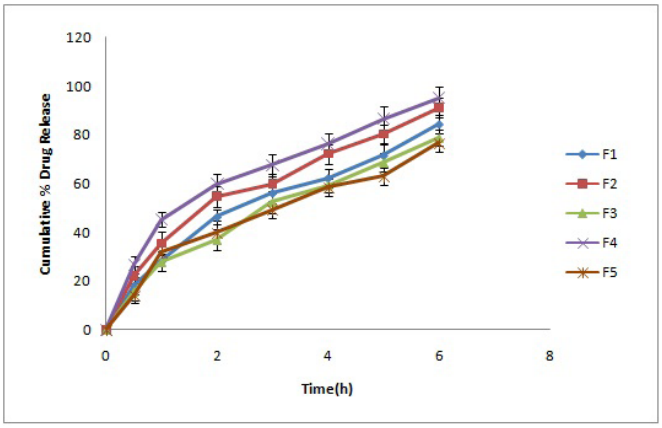

FIGURE 3 - I*n-vitro* release profile of hydralazine hydrochloride muco-adhesive buccaltablets.

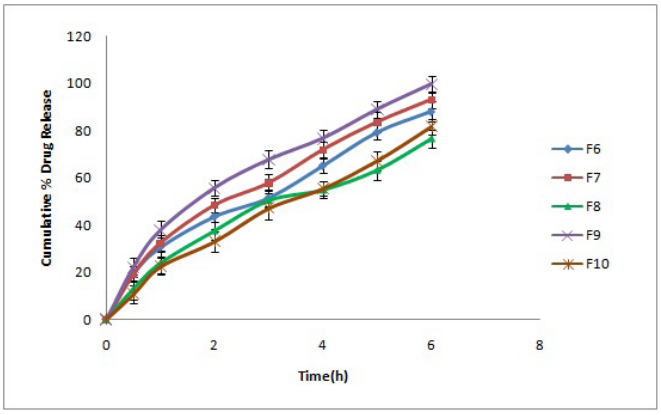

FIGURE 4 - *In-vitro* release profile of hydralazine hydrochloride muco-adhesive buccaltablets.

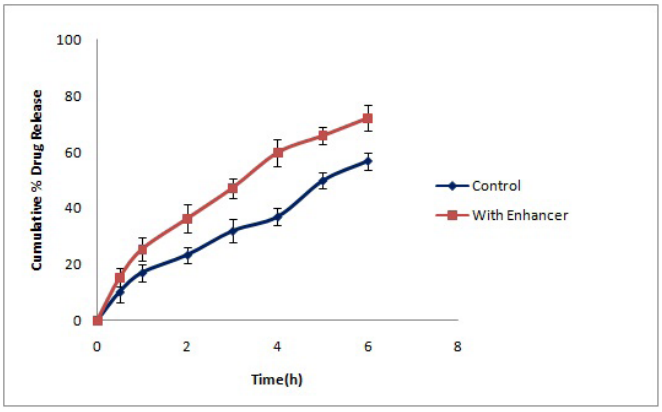

FIGURE 5 - *Ex-vivo* release profile of hydralazine hydrochloride muco-adhesive buccaltablets.

Ex-vivo permeation studies

Based on the drug release profile ex-vivo study was conducted using F9 formulation with PEG 6000 as permeation enhancer and control (without enhancer). The test drug release shown 71.09±1.61 as against 56.85±2.11.

Kinetics of drug release and mechanism

The release mechanism and kinetics of hydralazine hydrochloride formulations were to fit into mathematical models, r^2 values for zero order, first order, Higuchi and Peppas models were represented in Table VI. The higher R^2 values for Zero-order and Higuchi suggest that the drug release follows zero-order kinetics with diffusion mechanism.

Drug – excipient compatibility studies

FTIR analysis were conducted to determine the compatibility of drug and polymers used for the development of buccal tablets and presented in Figure 6. IR spectrum of pure drug exhibits characteristic peaks at 3455, 3025, 1174 and 1588, cm^{-1} due to N-H stretch, aromatic C-H, C-N and C=C stretching respectively. IR spectrum of carbopol 934P and HPMC K_4M formulation showed characteristics peaks at 3524, 3113, 1158 and 1592 cm^{-1} and carbopol 934P and Na CMC formulation showed characteristics peaks

Table VI - *In-vitro* release kinetics of the formulations

Formulation	Zero-order	First-order	Higuchi	Korsmeyer-Peppas	Hixson-crowel
F1	0.957	0.566	0.989	0.177	0.356
F2	0.923	0.507	0.995	0.203	0.333
F3	0.962	0.583	0.987	0.16	0.363
F4	0.89	0.479	0.992	0.227	0.324
F5	0.933	0.561	0.983	0.136	0.357
F6	0.965	0.566	0.983	0.197	0.354
F7	0.961	0.564	0.99	0.231	0.355
F8	0.961	0.607	0.982	0.151	0.375
F9	0.987	0.528	0.996	0.251	0.342
F10	0.932	0.661	0.961	0.183	0.398

at 3505, 3211, 1159 and 1533 cm^{-1}. The above peaks confirm that there was no disappearance or shift in peak position of hydralazine hydrochloride in spectra of drug and excipients in figures 6-8, which proved that drug and excipients were compatible.

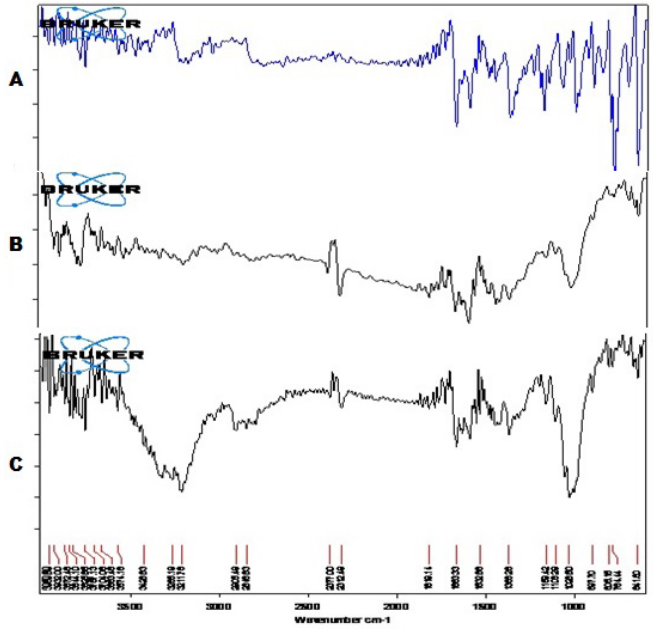

FIGURE 6 - FTIR spectrum of A) pure drug of Hydralazine hydrochloride B) Drug, carbopol 934Pand HPMC K4M C) Drug, carbopol 934P and Na CMC.

CONCLUSION

This study demonstrated that hydralazine hydrochloride could be delivered through the buccal route. Muco-adhesive tablets for buccal delivery of hydralazine hydrochloride could be prepared by using muco-adhesive polymers carbopol 934P, HPMC K4M and Na CMC. Development of muco-adhesive buccal tablets is one of the alternative routes of administration to avoid first pass metabolism and provide controlled release. Optimized formulation F9 containing ratio of polymers carbopol 934P to Na CMC portion 1:3 showed significant bioadhesive properties with an optimum release profile and could be useful for buccal administration of hydralazine hydrochloride. Formulation F9 exhibits controlled release with Higuchi release mechanism. Further, in vivo studies in animal models are required to prove the biological performance of the formulation.

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