Available online at www.ijpab.com

ISSN: 2320 – 7051
Int. J. Pure App. Biosci. **3 (2):** 95-104 (2015)

INTERNATIONAL JOURNAL OF PURE & APPLIED BIOSCIENCE

Research Article

OPEN ACCESS

Formulation and evaluation of chewable modified-release tablet containing sodium fluoride and vitamin C

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ABSTRACT

Chewable modified release tablets containing two active ingredients vitamin C (200mg) and Sodium Fluoride (2mg) were formulated for the treatment of dental diseases. Other ingredients include Mannitol, Carbopol and Hydroxyl-Propyl Methylcellulose (HPMC), in different ratios. These tablets were prepared by direct mixing of Hydroxypropyl Methylcellulose (HPMC), vitamin C, Sodium Fluoride, Carbopol, Mannitol and Magnesium Stearate by pressing through single punch machine. Their dissolution properties were assessed using USP (paddle apparatus).In order to investigate the mode of drug release from the tablets, the release data were subjected to various release kinetic models. The modified release strength of the tablets was also evaluated. The results showed that the combination of two polymers give a satisfactory drug release. This new formulation can be administered either by swallowing the whole tablet or by chewing the tablet beacause controlled release properties of this formulation do not change by chewing the tablet. Such type of tablets could be valuable for all patients including those who have difficulty in swallowing, for example pediatrics and geriatrics patients.

Keywords: *Modified release tablets, HPMC, carbopol, pediatrics, geriatric, Modified release Property.*

INTRODUCTION

Chewable modified release drug delivery systems[1] was basically developed to enhance retention time of the drug (taken orally)or to provide modified release of drugs. Different chewable modified release drugs reported earlier are miconazole , fungicidal agents and nystatin . This system has also been proposed for treating other sodium fluoride deficiencies such as periodontitis and generally employed as fluoride supplement. Among the most important oral diseases such as oral candidosis, this method of treatment is very useful. The use of other pharmaceutical dosage forms i.e. gels, solutions, mouthwashes and suspensions is not effective for candidosis, because the drugs in these dosage forms are removed quickly from oral cavity[2]. A multifactorial dental disease is one of the crucial problem of public health which can be prevented by Fluoride[3]. The approach for the formulation of modified releases[4] principally is based on the consumption of polymers (cellulose derivatives (Hydroxypropyl Methylcellulose [HPMC]) and Polyacrylic acid , Carbomer [CB]) of suitable physicochemical properties and the resultant formulation showed no interaction between polymer and the drug .Study has been revealed that the crystalline form of drug is present in polymer matrix. The result shows that tablets with suitable modified release properties can be prepared. It has been reported that Modified release system can be improved by using Carbopol and HPMC[5]. Perez Marcos et al. has demonstrated in one of his study that when combination of HPMC K4M and Carbopol was used with model drug (Propranolol hydrochloride), imbibitions of water in

Carbopol is lower than HPMC or their 1:1 mixture.HPMC and CP were extra granularly added without revealing of the fact that the polymers and fluid used in granulation to achieve compaction purpose, so the drug is diffused from the matrix with the help of HPMC[5]. Carbopol readily absorbs water and gets hydrated and swells. Carbopol is a candidate of choice for its use in control release drug formulation due to having properties like hydrophilic nature, insolubility in water and possession of crossed linked structure. By using Carbopol, tablets of low friability and excellent hardness is produced. The control release of conventional tablets[6] i.e. chewable tablets, sublingual tablets, swallow able tablets, sodium fluoride tablets, suppositories and effervescent tablets can also be obtained by the use of these polymers that will have a good binding characteristics. Zero-order kinetics and near zero-order kinetics[7] are observed by the tablets produced by the use of Carbopol polymer. This study has an aim of formulating a chewable modified release tablet (2 mg Sodium Fluoride, 200mg vitamin C) and Carbopol and Hydroxypropyl Methylcellulose (HPMC) for controlled release of Fluoride in oral cavity for a treatment of dental caries[3].

MATERIALS AND METHOD

Instrumentation

In this study following instruments were used: UV-Vis Spectrophotometer Shimadzu model 1800, Ultrasonicator, pH meter, electric water bath, and Digital balance(Shimadzu Japan, 0.001mg sensitivity)and glassware .

Materials used in this study

HPMC: (Trade Name: Hypromellose Shin - Etsu chemicals, co Ltd.,Japan)(HPMC 100,000 CP Hypromellose). Carbopol 943(BF Goodrich).

Sodium fluoride Powder

NaF (Riedel- de Haen-Germany). It is White hygroscopic, odorless powder, it is used widely in water fluoridation, in Small installations mainly. Direct method is used for fluoride measurement by the use of an analyzer and specific electrodes. (201 E. HANNA instrument, China) . Before the analysis of sample, different sets of standards (ranging from 0.025 to 3.2 ppm F) in triplicate was prepared, using serial dilution method from 100 ppm NaF stock solution (E.Merck, Darmstadt,Germany)

Vitamin C powder

Vitamin C powder was obtained from Ameer pharma as gift sample. Standard curve was measure by spectrophotometer which shown in figure 1 and FTIR spectra of blend also shown in figure 1.

Preparation of chewable modified release oral tablets:

Tablets formulation

The tablet was prepared by directly mixing sodium fluoride, vitaminC, hydroxypropyl methylcellulose, Carbopol, Mannitol and Magnesium Stearate. Mixing of this physical blend done in pestle and mortar for 15 mins. The mixture is then compressed by a single punch press of 8mm by directly compressing at 1500kg/cm^2 for not more than 5 seconds which results in circular biconvex tablets. Tablets of Sodium Fluoride and vitamin C were prepared by using Carbopol and HPMC alone and with combination as modified release polymers. Average weight of hundred tablets was obtained after weighing them individually and then calculations of Percentage deviation were performed and weight variation was checked. Vernier caliper was used to measure the thickness of these tablets. Samples were prepared. The ingredients of the tablets prepared listed as follows:

Statistical analysis

Different parameters and variables of the study were described through statistical analysis and their relationship with each other. For comparison of 2 groups Independent t-test of significant was used. Statistical evaluation of all data is achieved by the use of SPSS-10.

Table 1: Composition modified release tablet formulations

Formulation code	HPMC (Mg)	Carbopol (Mg)	Sodium fluoride (Mg)	Vitamin C (Mg)
F1	55	---	2	200
F2	----	55	2	200
F3	25	18	2	200
F4	25	25	2	200

Note: Mannitol, Lactose, Magnesium Serate and Talcum was in equal amount in all formulations

In vitro dissolution[8]

The dissolution tests were performed using the paddle method of USP 24 with the aid of dissolution apparatus rotating at 100 rpm. The dissolution medium was 900 ml phosphate buffer (pH 6.8) and the temperature was set at $37C^0$. Samples of the solution were withdrawn at definite time intervals. The dissolution media was then replaced by fresh dissolution fluid to maintain a constant volume. The solution was passed through a filter and then the concentration of vitamin C in solution was measured with an ultraviolet spectrophotometer at a wavelength of 255 nm. The concentration of sodium fluoride was determined by conductivity meter .The test was carried out in triplicate and the results expressed as mean ± standard deviation (SD).

Analysis of drug release kinetics[9]

In order to investigate the mode of drug release from the tablets, the release data were subjected to the following release models: zero order, first order, square root of time and Korsemeyer-Peppas, as shown in Eqs 1 – 4, respectively.

$Q = kot$ ..... (1)

$\ln (100 - Q) = \ln Q0 - k1t$ ..... (2)

$Q = kHt1/2$…….…..…….. (3)

$Q = kptn$ …….…..…….. (4)

Where Q is drug released at time, t, while k0, k1 and kH are coefficients of the respective equations; kp is a constant incorporating structure and geometric characteristics of the release device; and n is the release exponent indicative of the mechanism of release. When n approximates to 0.5, a Fickian/diffusion controlled release is implied; $0.5 < n < 1.0$ indicates non-Fickian transport; and $n = 1$ is zero order (case II transport). When the value of n approaches 1.0, it can be said that release approximates zero order.

Compatibility studies[10]

The drug-polymer compatibility studies were carried out using Infrared Spectrophotometer (IR). Infra-red spectra of pure drug and mixture of drug and excipients were recorded.

Thickness[11]

The thickness of three randomly selected tablets from each formulation was determined in mm using a Vernier caliper (Pico India). The average values were calculated.

Content uniformity[12]

Ten tablets from each formulation were taken, crushed and mixed. From the mixture 2 mg of Sodium fluoride equivalent of mixture was extracted thoroughly with 100 ml of pH 6.8 phosphate buffer and checked through conductivity meter and compare with standard solution . The amount of drug (vitamin C) present in each extract was determined using UV spectrophotometer at 255 nm.

Microenvironment pH[13]

The microenvironment pH (surface pH) of the sodium fluoride tablets was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Battenberg , was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose.

The tablet was allowed to swell by keeping it in contact with 5 ml of distilled water (pH 6.5 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min.

Swelling study[14]

Six Sodium fluoride and vitamin C containing tablets were individually weighed (W1) and placed separately in Petri dishes with 5 ml of phosphate buffer of pH 6.8. At the time interval of 1, 2, 4, and 6 h, tablet was removed from the Petri dish and excess water was removed carefully using the filter paper. The swollen tablet was then reweighed (W2) and the percentage of hydration was calculated using the following formula. Percentage hydration = [(W2-W1)/ W1] ×100

Calibration Curve of vitamin C

The calibration curve of vitamin C in phosphate buffer (pH 7.4) using U.V. spectrophotometer at 255 nm has been shown in Fig 6 and its absorption values are in Table 7.

RESULTS AND DISCUSSION

Melting Point

The melting point of the drug was observed by capillary fusion method. The observed melting point of the drug was found to be in the range of reference value. The results are shown in Table 2.

Table 2: Melting point vitamin C

Apparatus	Observed value	Reference value*
Melting point apparatus	191°C ± 1.28	190-198°C

Compatibility studies

The incompatibility between the drug and excipients were studied by FTIR spectroscopy. The spectral data of pure drug (vitamin C) and various drug-excipient mixtures were presented in Fig. 2. The results indicate that there was no chemical incompatibility between drug and excipients used in the formulation.

Weight variation test

The weight variation test was conducted for each batch of all formulations F1 to F4 as per USP and the results shown in Table 3. The weight variation test for all the formulations complies with the USP limit (± 10%).

Hardness test

The adequate tablet hardness is necessary requisite for consumer acceptance and handling. The measured hardness of the tablets of each batch of all formulations i.e. F1 to F4 were ranged between 3.0 to 7.0 Kg/Cm^2 and the results are shown in Table 3.

Friability test

The friability test for all the formulations were done as per the standard procedure USP. The results of the friability test were tabulated in Table 3. The data indicates that the friability was less than 1% in all formulations ensuring that the tablets were mechanically stable.

Thickness

The thickness of the tablets was found to be almost uniform in all formulations F1 to F4 in the range of 2.5 to 3.0 mm. None of the formulations (F1 to F4) showed a deviation. Hence, it is concluded that all the formulations complied the thickness test and the results are shown in Table 3.

Drug content

The drug content of each batch of all the formulations was evaluated as per standard protocol and the results are shown in the Table 3. The results indicate that the percentage of drug content was found to be 98.00% to101.00%. Hence it is concluded that all the formulations are following the acceptable limits as per USP i.e.± 5%.

Surface pH

Surface pH of all the tablets F1 to F4 was found to be 5.8 to 6.3, which is well within the limit of acceptable salivary pH range of 5.69 to 6.34 (Table 6). Hence, it was concluded that all formulations could not produce any local irritation to the mucosal surface.

In-vitro release studies

The formulations F1, F2, F3 and F4 containing drug, Carbopol and HPMC in different ratio respectively. The *in vitro* cumulative drug release profile of formulations F1, F2, F3 and F4 showed 63%, 71%, 98% and 96%, respectively in 6h (sodium fluoride). Among these four formulations, F4 was found to be minimum percentage drug release. During the study it was observed that the tablets were initially swelled and no erodible over the period of 6h (Fig. 3 and 4).Similarly the formulations F2 containing alone HPMC polymer and it was found maximum drug release. It was concluded that by use of combination of two polymers Carbopol and HPMC in the formulation, the drug release rate from the tablets was found to be decreased. But when the both polymer carbopol and HPMC used alone in maximum concentration, the drug release rate was found to be increased. This may be due to increased hydration (or) swelling characteristics of polymers with increased concentrations. The *in vitro* cumulative drug release profile of formulations F1, F2, F3 and F4 showed 73%, 81%, 98% and 86%, respectively in 6h (vitamin C).

Fig. 1: UV spectrum of vitamin C

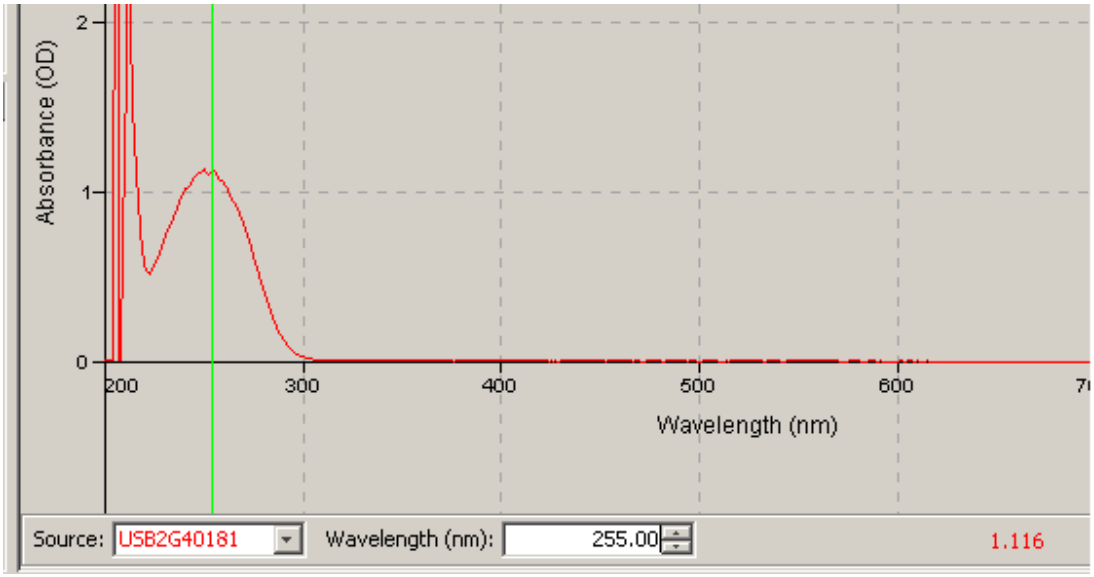


Fig. 2: IR of Vitamin C, HPMC and Carbopol

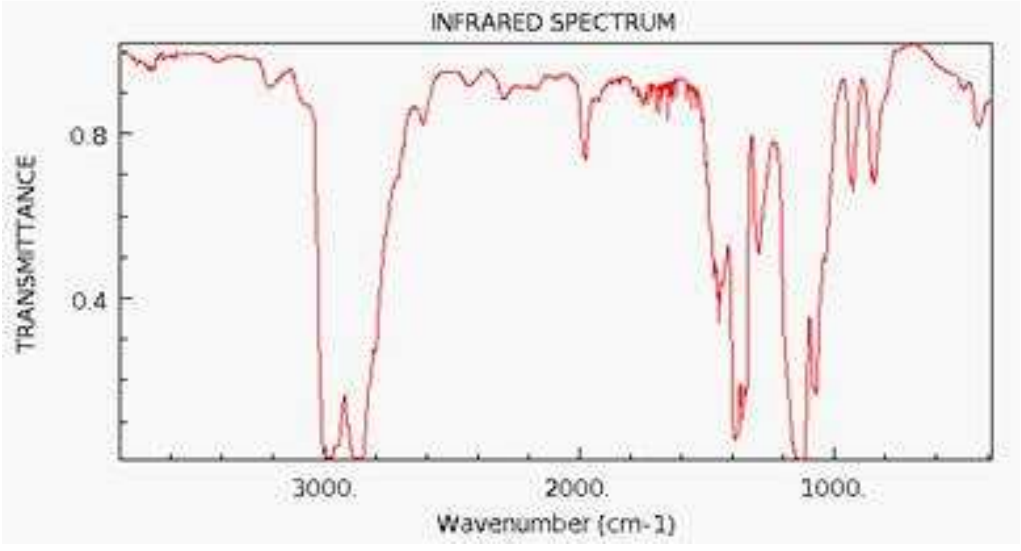


Table 3: physical parameters

Formulation	Weight (mg)	Hardness (Kg/cm2)	Friability (%)	Thickness (mm)	Drug contents (%)	
					NaF	Vit C
F1	200	6.7	0.5	3.20	98.3	102.4
F2	210	6.9	0.3	3.10	97.3	99.3
F3	200	5.9	0.4	2.90	98.4	101.3
F4	210	7.3	0.2	3.05	97.3	98.4

Table 4: drug release profile of sodium fluoride

Formulation	1hr	2hr	4hr	6hr
F1	12.8	23.5	37.6	63.5
F2	8.5	15.6	44.7	71.3
F3	18.5	25.7	54.6	98.8
F4	23.6	31.5	62.5	96.6

Fig. 3: Release Profile of sodium fluoride in different formulations

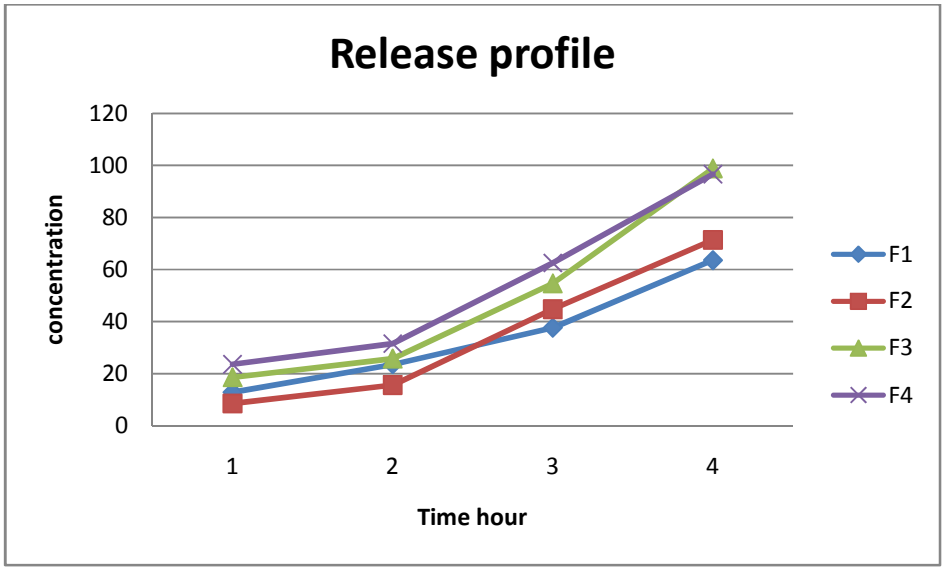


Table 5: drug release profile of vitamin C

Formulation	1hr	2hr	4hr	6hr
F1	12.8	23.5	57.6	73.5
F2	17.5	35.6	44.7	81.3
F3	18.5	25.7	54.6	98.8
F4	23.6	31.5	62.5	86.6

Fig. 4: Release Profile of vitamin C in different formulations

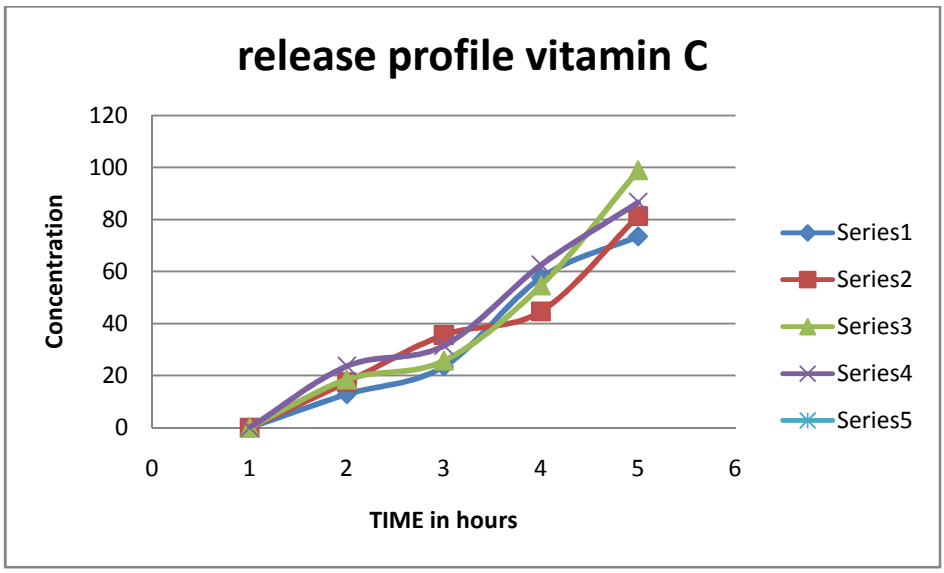


Table 6: pH range of different formulations

Formulation	2hr	4hr	6hr
F1	5.71	6.34	6.38
F2	5.91	6.12	6.18
F3	5.87	5.97	6.21
F4	5.73	5.86	6.54

Fig. 5: pH-profile of different formulations

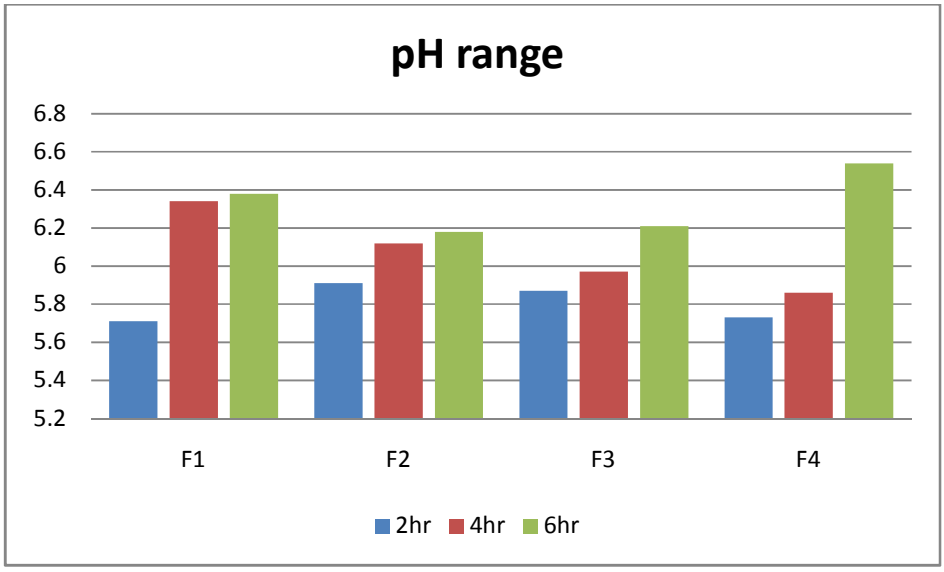


Table 7: Observation table for standard curve of vitamin C by UV Spectrophotometer

S. No.	Concentration (µg/ml)	Absorbance Phosphate buffer (pH 7.4)
1	5	0.078±0.0005
2	10	0.140±0.0019
3	15	0.203±0.0022
4	20	0.265±0.0017
5	25	0.327±0.0004
6	30	0.381±0.0027

Fig. 6: standard curve of vitamin C by UV spectrophotometer

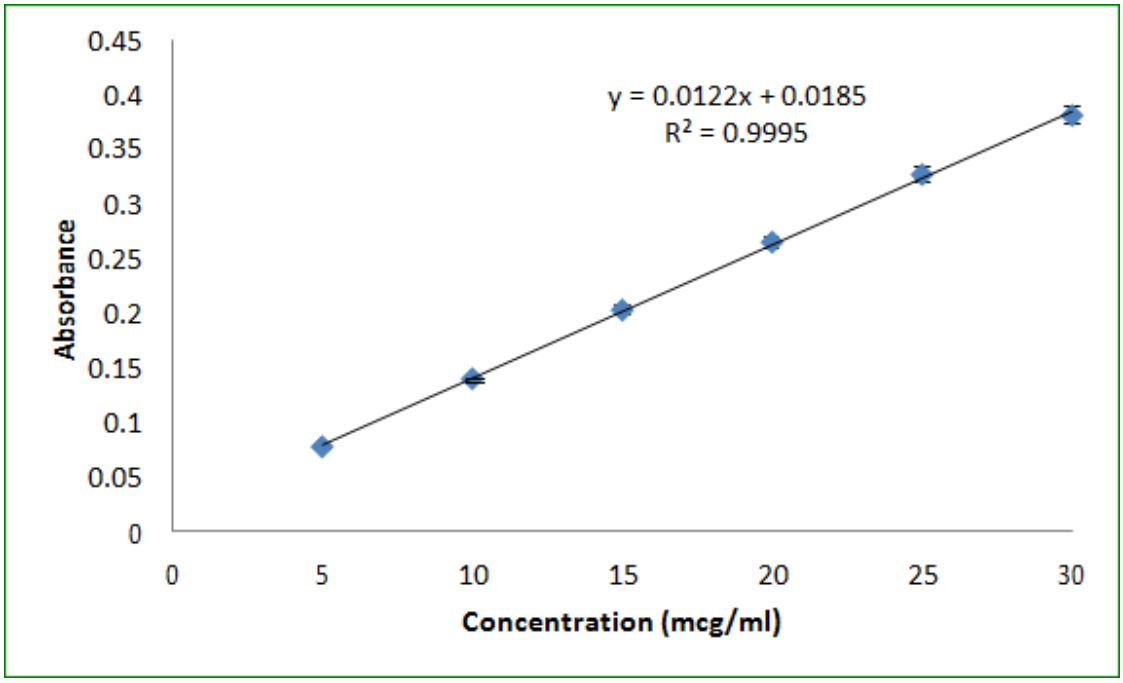
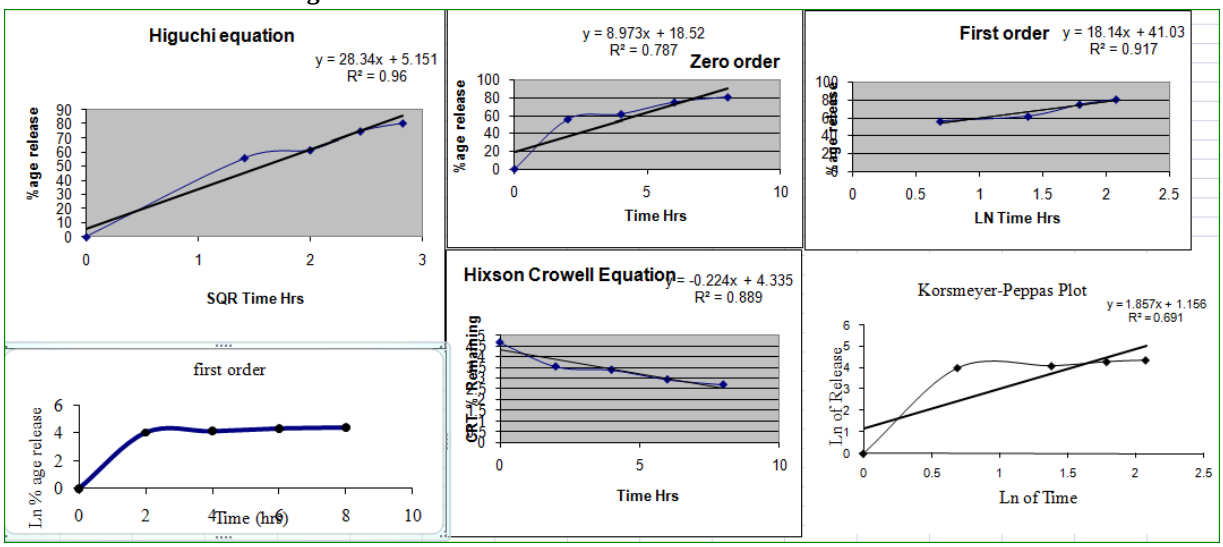


Table 8: Swelling index of optimized formulation (F4)

Time (hrs)	Swelling Index (%)*
	F4
0	0
0.5	11.9
1	27.6
2	35.3
3	46.3
4	52.11
5	60.2
6	82.3

Fig. 7: Kinetic Profile for *in-vitro* release of F4 formulation



Stability studies

The selected formulation containing a HPMC/Carbopol 1:1 ratio (batch F4) was subjected to accelerate the storage conditions (40 ± 2 °C/75 ± 5% RH for 6 months). Formulation was analyzed for organoleptic characteristics, hardness and dissolution. Similarity factor f2 was calculated to compare the dissolution profiles according to equation

$$f_2 = 50 \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]\times 100\right\}$$

Tt and *Rt* are the percent drug dissolved at each time point for test and reference. Three tablets of F4 were subjected to this study and all the tablets found accurate.

CONCLUSIONS

Sodium Fluoride and vitamin C containing chewable modified release tablets could be formulated using the polymers , Carbopol and HPMC with the ratios of 1:1 or alone . It can be seen that by increasing the concentration of HPMC/ Carbopol alone in the formulation, the drug release rate from the tablets was found to be unsatisfactory. When combination of two polymers was used, the drug release rate was found to be decreased. The *in vitro* release kinetics studies reveal that F4 formulations fits well with first order kinetics followed by Korsmeyer-Peppas, first order and then Higuchi's model and the mechanism of drug release is non-Fickian diffusion

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