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Full Length Research Paper

Application of κ-carrageenan as a sustained release matrix in floating tablets containing sodium salicylate

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The main aim of the present investigation was to develop sustained release (SR) floating drug delivery system (FDDS) of sodium salicylate using k-carrageenan as the sustained release matrix. Varying w/w concentration ratios of drug and polymer dispersion ranging from 1:0 to 1:1 were selected from the preliminary trials for this investigation made from batches granulated with isopropyl alcohol containing, in addition, the same w/w concentration of: PVP K30; magnesium stearate and talc. Equal concentrations of citric acid and optimum concentration of sodium bicarbonate in the various batches were used to induce the generation of CO_2. The physical properties of the various matrices were studied. The *in vitro* buoyancy lag time (BLT), total floating time (TFT) and *in vitro* drug release of the tablets were studied in 0.1 N HCl. The results show that BLT ranged from 50 to 55 s, while the TFT were significantly higher than 12 h ($p < 0.05$) for most batches. Results of *in vitro* release show that about 97, 80, 86.1, 53.4, 64.4 and 47.7% of drug were released at 6 h, respectively from batches F1, F4, F5, F6, F7 and F8. Therefore, carrageenan presented good matrix for the formulation of sustained release sodium salicylate floating tablets and could be used at ratios 1: 0.87, 1: 0.67 and 1: 0.53 (drug: polymer) combination for SR sodium salicylate tablets.

Key words: Carrageenan, bio-adhesion, sustained release, floating drug delivery, nonsteroidal antiinflammatory drugs (NSAIDs).

INTRODUCTION

Carrageenan is a high molecular weight sulphated polysaccharides obtained from certain species of red seaweeds belonging to the class Rhodophyceae (Nerurkar et al., 2005; Coviello et al., 2007). Based on the number of sulphate groups per repeat unit of polysaccharide, it is classified into three different grades: kappa (κ), iota (ι) and lambda (λ) with one, two or three sulphate groups, respectively (Yuguchi et al., 2002; Farnoosh et al., 2011). Carrageenan produces a thermo reversible sol-gel in aqueous solution which undergoes dispersion following random-coil formation in the sol stage. At low temperature, galactose sequence within the carrageenan chains twist in a double helix fashion (Tari et al., 2009). The sweet taste of galactose may help to mask the bitter taste of some drugs thus avoiding the need for flavouring and sweetening agents (Farnoosh et al., 2011). Carrageenan provides several sites for hydrogen bonding which impart bio-adhesive properties to the final formulation (Farnoosh et al., 2011). K-carrageenan's functionality in pharmaceuticals, nutraceuticals and cosmeceuticals depends on molecular weight and these functionality may be lost if it is hydrolysed to a molecular weight below 100 kDa. Current health concerns focus on carrageenan of molecular

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weight below 100 kDa, claimed to be toxic. However, high-molecular weight carrageenan (100 to 800 kDa) do not hydrolyse under physiological conditions to such fractions (Necas and Bartosikova, 2013)

One of the novel approaches in the area of oral sustained release drug delivery is gastro retentive drug delivery system (GRDDS) (Londhe et al., 2010). GRDDS prolongs the retention time of dosage forms in the stomach or upper gastrointestinal tract (GIT), as to improve solubility, bioavailability and the therapeutic efficacy of the drugs (Talukder and Fassihi, 2004). Approaches to preparation of GRDDS include floating systems, swellable and expandable systems, high density systems, bio-adhesive systems, altered shape systems, gel forming solution or suspension system and sachet systems. Among these, the floating dosage form has been used most commonly. The floating systems include gas-generating systems, non effervescent systems and raft forming systems (Patel et al., 2006). Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (Babu and Khar, 1990; Mayavanshi and Gajjar 2008). Floating drug delivery offers several applications for drugs having narrow absorption window in the upper part of the GIT. It retains the dosage form at the site of absorption and thus enhances the bioavailability (Babu and Khar, 1990; Mayavanshi and Gajjar, 2008).

Sodium salicylate is associated with GIT side effects including gastric and duodenal ulceration. The development and fabrication of modified release dosage forms of the drug are attempts to improve therapeutic efficacy and reducing the severity of GIT side effects. Wang et al. (2003) in a study observed that aspirin and salicylates, at 100 to 180 µg/ml, had inhibitory effects on *Helicobacter pylori* and increased its susceptibility to amoxicillin, clarithromycin and metronidazole. Both drugs are rapidly metabolized and the required dose for these effects is reached transiently. The effectiveness of the salicylate concentrations required for these effects can be achieved through tailored sustained release formulation. The aims of the work are to formulate sustained release effervescent floating tablets containing sodium salicylate and to study the properties of the formulations.

MATERIALS AND METHODS

Chemicals

Sodium salicylate, PVP K30 (Sigma–Aldrich, Germany), k-carrageenan, isopropyl alcohol (Sigma Aldrich, Germany), magnesium stearate, talc, sodium bicarbonate, citric acid, hydrochloric acid, sodium chloride (Loba Chemie Pvt. Ltd. Mumbai, India), distilled water (UNN, Water Resources, Nigeria). All other reagents and solvents were analytical grade and were used as supplied.

Preparation of granules

Sodium salicylate granules were prepared by wet granulation method using PVP K30 as the binder at concentration of 4% w/w in sufficient isopropyl alcohol as the granulating fluid. Carrageenan was used as the polymer and sustained release matrix at different concentrations as presented in Table 1. A constant value of 20 mg of citric acid added across all batches and optimum concentration of 40 mg of sodium bicarbonate in batches F1, F2 and F4 to F8 were used to induce generation of CO_2 in the presence of the dissolution medium. Batch F2 was formulated as control without sodium bicarbonate. Batch F9 was formulated with 60 mg of sodium bicarbonate and less concentration (120 mg) of the polymer while batches F8 had 40 mg of sodium bicarbonate and 80 mg of polymer to see the concentration effects on polymer gel formed by hydration following the release of CO_2. The powders were mixed for 10 min in a Rotomixer (Forster Equipment Co Ltd, Whestone, Leicester, England) and moistened with the 10 ml of isopropyl alcohol. The wet mass was screened with a 1.7 mm sieve, dried in a hot air oven at 60°C for 1 h (Memmer, U25, Western Germany) and finally sieved with a 1.0 mm sieve.

Preparation of tablets

The sodium salicylate granules were mixed with the lubricants and glidents (2.5% w/w magnesium stearate and 1% w/w talc) and compressed at 45 Kgf using an automated F3 Manesty Single Punch tabletting machine.

Evaluation of tablets

Dimensional characteristics

Tablet thickness and diameter was determined using venier caliper to measure twenty tablets randomly selected from each batch of the tablets.

Uniformity of weight

The British Pharmacopoeia (BP) (2009) method was employed in the weight uniformity test. Twenty tablets were randomly selected from each batch. The tablets were weighed together and individually using an electronic balance (Ohaus Adventurer, China) and the percentage deviations were determined.

Tablet friability test

Friability test was determined using a friabilator (Erweka GmbH, Germany) rotated at 25 rpm for 4 min as stipulated in British Pharmacopoeia (2009). The tablets were weighed before and after rotation and the percentage friability calculated using:

$$\text{Friability} = 1 - \frac{W_f}{W_o} \text{ x } 100 \quad (1)$$

Table 1. Composition of sodium salicylate floating matrix tablets.

Ingredients	Formulation code/quantity per tablet (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sodium salicylate	150	150	150	150	150	150	150	150	150
k-Carrageenan	160	-	160	150	140	130	100	80	120
Drug: Polymer ratio	1:1.1	1:0	1:1.1	1:1	1:0.93	1:0.87	1:0.67	1:0.53	1:0.8
Sodium bicarbonate	40	40	-	40	40	40	40	40	60
Citric acid	20	20	20	20	20	20	20	20	20
PVP K30	16	16	16	16	16	16	16	16	16
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	4	4	4	4	4	4	4	4	4

FI-F9: Formulations of sodium salicylate tablets.

Where W_o and W_f are the initial and final weights of the tablets, respectively.

Crushing strength test

This test was carried out using a Monsanto hardness tester. Ten tablets from each batch were randomly selected and the hardness was determined by diametrical compression and breaking of tablets.

In vitro buoyancy lag time (BLT) and total floating time (TFT)

In vitro buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a beaker containing 300 ml of 0.1 N HCl maintained at 37 ± 0.5°C. The time required for the tablet to rise to the surface and float was determined as buoyancy lag time, while the duration during which the tablet remains floating was determined as total floating time.

***In vitro* release studies**

Beer's calibration curve for sodium salicylate was obtained at a concentration range of 0.1 to 0.8 mg/ml in 0.1 N HCl at a predetermined wavelength of 290 nm. The *in vitro* dissolution profile for each batch of tablets was determined using the paddle method (BP, 2009), with an Erweka DT 600 dissolution apparatus. About 900 ml of freshly prepared 0.1 N HCl maintained at 37 ± 0.5°C was used. The paddle was rotated at 100 rpm. At various predetermined intervals, 5 ml sample was withdrawn from the dissolution medium, filtered with a non adsorbent filter paper (Whatman no. 1) and assayed at a maximum wavelength of 290 nm using spectrophotometer (Jenway 6305, UK). An equal volume of the withdrawn sample was replaced with a fresh medium to maintain sink condition.

Kinetic analysis of *in vitro* release profiles

Four kinetic models including the zero-order, first order equation, Higuchi square root equation and Korsmeyer-Peppas empirical model were applied to the *in vitro* release data.

$$Q = k_0 t \quad (2)$$

$$Q = 100\ (1 - e^{-K_1 t}) \quad (3)$$

$$Q = K_2\ (t)^{1/2} \quad (4)$$

$$M_t/M_\infty = K_3 t^n \quad (5)$$

Where Q is the release percentage at time t and K_0, K_1, K_2 and K_3 are the rate constants of zero-order, first-order, Higuchi and Korsmeyer-Peppas models, respectively (Higuchi, 1963; Umeyor et al., 2012; Chime et al., 2013). M_t/M_∞ is fraction of drug released at time t, n is diffusion exponent and is indicator of the mechanism of transport of drug through the polymer, k is kinetic constant (having units of t^{-n}) incorporating structural and geometric characteristics of the delivery system. The release exponent n = 0.5 and 1.0 for Fickian and non-Fickian diffusion, respectively (Korsmeyer et al., 1983).

Statistical analysis

All values are expressed as mean ± standard deviation (SD). Data were analysed by one-way analysis of variance (ANOVA). Differences between means were assessed by a two-tailed student's T-test. $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Dimensional properties

From the values of dimensional properties of sodium salicylate floating tablets shown in Table 2, the tablets showed stable dimensional properties. The tablets showed stable diameter of 0.8 mm and uniform thickness of 0.04 mm, except batch F8, which exhibited higher thickness of 0.05 mm. However, the low standard deviation of the dimensional properties confirmed the reproducibility and reliability of this formulation and the method of production.

Table 2. Properties of sodium salicylate sustained release floating tablets.

Tablet code	Diameter (mm)*	Thickness (mm)*	Weight (mg)*	Hardness (kgf)[a]	Friability (%)*	Buoyancy lag time (Sec)	TFT (h)
F1	0.83±0.005	0.04±0.005	403.5±0.53	4.65±0.53	1.60	50	>12
F2	0.82±0.008	0.04±0.008	400.4±0.68	4.85±0.53	0.50	Non floating	Failed
F3	0.81±0.005	0.04±0.006	402.4±0.I6	4.50±0.47	0.90	Non floating	Failed
F4	0.81±0.003	0.04±0.007	400±0.91	4.45±0.28	1.00	50	>12
F5	0.81±0.004	0.04±0.010	400.7±0.11	4.75±0.42	0.10	54	>12
F6	0.81±0.005	0.04±0.007	402.8±0.80	4.65±0.58	0.50	57	>12
F7	0.81±0.004	0.04±0.006	404.1±0.91	4.90±0.52	0.80	54	>12
F8	0.81±0.005	0.05±0.005	405.3±0.83	4.60±0.61	1.00	153	>12
F9	0.81±0.004	0.04±0.008	404.7±0.98	4.45±0.50	0.20	180	>6

*Mean for 20 tablets ± SD, [a] Mean for 10 tablets ± SD, SD: Standard deviation; TFT: Total floating time.

Uniformity of weight

Weight uniformity test was performed on the sustained release effervescent floating tablets so as to determine its compliance with BP (2009) specifications. Variation in weight of tablets causes variation in drug content which will also affect the bioavailability of the drug. The result of tablet weight uniformity test presented in Table 2 showed that the tablets complied with BP (2009) specifications, as their percentage deviations were significantly lower than 5% ($p < 0.05$).

Tablet friability

The sodium salicylate sustained release tablets based on floating drug delivery system exhibited good friability results. Values of friability range of 0.8 to 1% are quoted as upper level of acceptance for tablets prepared by wet granulation (BP, 2009). From Table 2, the batches of the sodium salicylate tablets complied with BP standards for friability test however, batch F1 showed friability of 1.6%. The results showed that the tablets can effectively withstand handling, packaging and transportation without showing any form of defect.

Hardness/crushing strength test

The results of crushing strength test are presented in Table 2, and show that all the tablet batches complied with the BP specifications for crushing strength test of ≥ 5 kgf. Tablets hardness ranged from 4.45 ± 0.50 to 4.90 ± 0.52 kgf. The results showed that the mechanical properties of the tablets will not be compromised during long term storage. The tablets will effectively withstand the processes of handling, packaging and transportation without breaking.

In vitro buoyancy lag time (BLT) and TFT

The results of BLT and total floatation time (TFT) respectively shown in Table 2 indicate that the floating lag time (FLT) of the tablets batches F1, F4, F5, F6, F7 and F8 containing 1:1.1, 1:1, 1:0.93, 1: 0.87, 1:0.67 and 1: 0.53 of drug: carrageenan were higher than 12 h. Also, batch F9 having 1:0.8 of drug to polymer ratio had TFT of greater than 6 h. These results show that the tablets had good floatation time in 0.1 N HCl. However, batches F2 (containing no polymer) and F3 without sodium bicarbonate failed to float as shown in Table 2. The results of the BLT ranged from 50 to 180 s. However, tablet excipients influenced the BLT just like the TFT. Absence of carrageenan in the formulations of the tablets (F2) caused a failure of floatation. This may be due to the absence of hydrogel matrix that entraps the CO_2 needed to maintain buoyancy. Also, batch F3 without sodium bicarbonate also failed to float in the medium used, this may be due to absence of CO_2 required to maintain buoyancy in the system. Batches F8 and F9, with lower concentration of carrageenan and 40 and 60 mg of sodium bicarbonate, respectively had higher FLT. This may be due to low concentration of the gel forming polymer as it was seen in the preliminary formulations that 40 mg of sodium bicarbonate was optimal for floatation. Therefore, the floating matrix tablets developed would prolong gastric residence time, increase bioavailability and reduce gastric irritation, otherwise rapid gastrointestinal transit may result to incomplete drug release and diminished pharmacological effects. Carrageenan would help to retain the dosage form at the site of absorption and thus enhances the bioavailability of this drug (Babu and Khar, 1990; Mayavanshi and Gajjar,

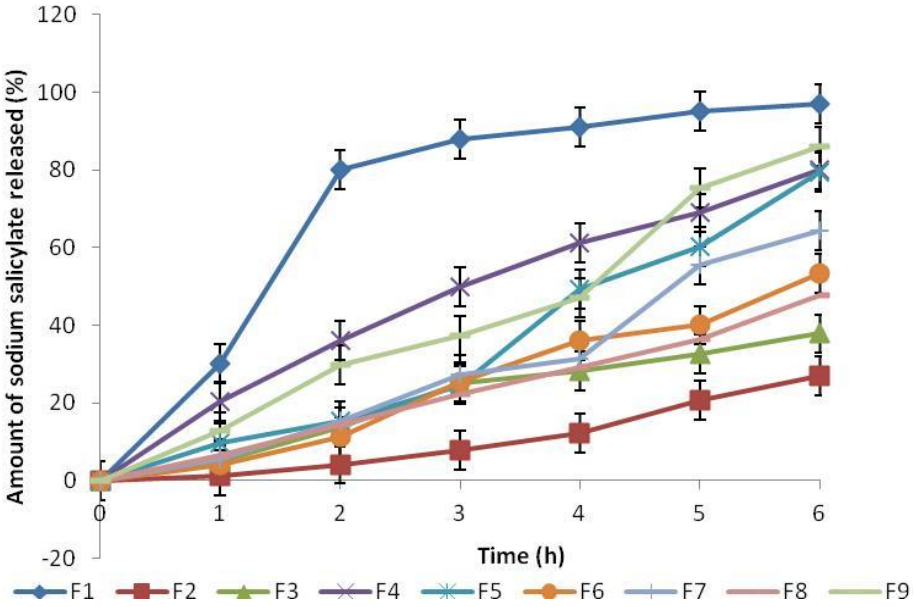

Figure 1. *In vitro* release of sodium salicylate in 0.1 N HCl. F1 to F9 represents various formulations of sustained release floating and non floating sodium salicylate tablets.

2008). Carrageenan provides several sites for hydrogen bonding as earlier stated which imparts bio-adhesive properties to the final formulation (Farnoosh et al., 2011). In addition, if the matrix escapes to the intestine, the muco-adhesive property could be further enhanced by the negative charge of the sulphate group in the carrageenan structure, forming ionic bonds with the positively charged mucin (Farnoosh et al., 2011) present on intestinal mucosa, thereby targeting this drug to the colon and improving its absorption while at the same time inhibiting gastric irritation due to dose dumping.

In vitro release studies

The *in vitro* release of sodium salicylate from the floating matrix system is presented in Figure 1. The results showed that the tablet formulations showed substantial sustained release properties in all the formulations. However, batch F1 exhibited burst effect with about 80% drug release at 2 h. This may be due to high carrageenan content of the tablets. The *in vitro* dissolution studies of sodium salicylate tablets based on floating drug delivery systems was affected by the excipients used during formulation. Batch F2 without carrageenan exhibited lower drug release rates significantly different from other batches, with about 27% drug release at 6 h ($p < 0.05$); this may be due to the absence of hydrogel matrix that entraps the CO_2 needed to maintain buoyancy, causing a decrease in amount of drug released in the medium. However, batch F9 showed about 86% drug release at 6 h. This may be due to high concentration of sodium bicarbonate in the tablets which generated high CO_2 causing higher drug release from the matrix tablet. About 97, 80, 86.1, 53.4, 64.4 and 47.7% of drug were released at 6 h, respectively from batches F1, F4, F5, F6, F7 and F8 containing 1:1.1, 1:1, 1:0.93, 1: 0.87, 1:0.67 and 1: 0.53 of drug: Polymer. The results showed that drug release varied directly with polymer concentration. Batches F6, F7 and F8 with 1:0.8, 1:0.67 and 1:53 of drug to carrageenan had significantly higher sustained release properties ($p < 0.05$) than other formulations containing high polymer concentrations. These results are in agreement with earlier researches performed with carrageenan in various sustained release tablets, where it was found that drug release was affected by the ratio of drug to carrageenan concentration (Gupta et al., 2001; Carien et al., 2009).

Drug release kinetics and mechanisms

The drug release mechanisms and release kinetics of the tablets were studied using four kinetic models including the zero-order, first order, Higuchi model and Korsmeyer-Peppas model. The results presented in Table 3 indicated that the zero-order plots for all the batches were linear except in batch FI ($r^2 \geq 0.9$). This showed that most

Table 3. *In vitro* release kinetics of sustained release sodium salicylate tablets.

Batch	Zero order (r^2)	Higuchi (r^2)	Higuchi (*n*)	First order (r^2)	Korsmeyer-Peppas (*n*)
F1	0.765	0.758	0.610	0.949	0.690
F2	0.937	0.903	1.688	0.930	1.671
F3	0.970	0.983	1.109	0.963	1.185
F4	0.977	0.998	0.756	0.984	0.780
F5	0.963	0.916	1.217	0.898	1.165
F6	0.980	0.973	1.453	0.973	1.481
F7	0.964	0.931	1.364	0.927	1.364
F8	0.994	0.969	1.088	0.978	1.076
F9	0.977	0.933	1.045	0.889	1.018

F1-F9: various formulations of sodium salicylate sustained release tablets based on floating drug delivery system; r^2: Regression coefficient; *n*: Slope.

of the batches followed zero-order release kinetics in agreement with most sustained release tablets formulated with carrageenan as sustained release matrix (Gupta et al., 2001; Carien et al., 2009). Higuchi plot of amount of drug release (Q) against square root of time was linear for all the batches of sodium salicylate tablet formulations except batch FI which showed non linear value. The plot of log Q versus log t according to Higuchi model showed *n* values that were above 0.5 which confirmed that diffusion controlled process was not the only mechanism of drug release (Higuchi, 1963; Chime et al., 2013).

The First order plots were linear; however, batches F5 and F8 were not linear. This showed that the release mechanism was of mixed order. The Korsmeyer–Peppas model for the tablets showed that most of the batches of sodium salicylate followed zero-order release models with *n* values of 1.0, therefore, the drug release in those formulations were independent of concentration. However, batches FI and F4 tablets exhibited non-Fickian (anomalous) diffusion release mechanism $0.5 < n < 1.0$, this showed that drug release followed both erosion and diffusion controlled process (Korsmeyer et al., 1983). Therefore, the mechanisms of drug release from sodium salicylate sustained release tablets showed mixed mechanism of release with diffusion and erosion process as the predominant mechanisms in batches F1 and F4 tablets and diffusion and dissolution controlled process in other batches. However, batch F1 tablets followed dissolution controlled process.

Conclusion

The k-carrageenan presented good gastro retentive matrix for the delivery of sodium salicylate. The formulations exhibited sustained release of the drug and the optimized formulations could be used for once daily administration. The properties of tablets studied showed that sodium salicylate tablets based on floating drug delivery system showed good mechanical properties. The *in vitro* release was affected by the composition of the tablet excipients. Increase in sodium bicarbonate concentration increased the release of drug from the matrix and also increased the buoyancy lag time, while increase in carrageenan content increased the drug release. Therefore, floating matrix drug delivery systems are potential delivery system for sustained release of sodium salicylate and could enhance patients' compliance, reduce frequency of drug administration, improve oral bioavailability and reduce the gastric irritation tendency of this drug due to circumvention of dose dumping and release in the stomach region.

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