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PREPARATION AND *IN VITRO* EVALUATION OF *IN SITU* GELLING GASTRORETENTIVE SALBUTAMOL SULFATE LIQUID FORMULATIONS

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Floating, Gastroretentive, *In situ* gelling, Salbutamol sulfate, Sodium alginate.

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ABSTRACT: Salbutamol is a selective β2-adreno-receptor stimulant and is given four times daily in a dose of 2.4 mg orally to maintain therapeutic blood level. It is known to be absorbed in proximal parts of the small intestine. Prolonging gastric residence time is, therefore, beneficial to improve its bioavailability. Hence, seven *in situ* gelling liquid formulations were prepared using sodium alginate (SA) as gel forming agent and HPMC as viscosity enhancer. $CaCO_3$ was incorporated as cross-linker and floating agent. Gelling capacity was evaluated based on a graded response which indicates rapidity of gelation and time taken by the gel to dissolve. All the formulations showed instant gelation but with regard to integrity, all formulations except the one with lowest SA level formed stiff gels maintaining integrity for at least 12 hr. With respect to floating behavior, all formulations except the one with the lowest SA level floated for more than 12 hr irrespective of their composition. Most of the formulations took less than 1 min to float but those with the lowest SA and $CaCO_3$ levels floated after about 2 min. Drug release study revealed release retarding behavior of the formulations and noticeable burst release. This effect was reduced at higher concentration of SA and $CaCO_3$. Release retarding effect of SA was only marginal at higher concentrations. $CaCO_3$ showed a similar effect but at higher levels insignificant change in release was observed. The drug release process, in all cases, best fits first order kinetics (R2 ranged between 0.932 and 0.991) and in most cases it seemed to occur by non-Fickian mechanisms ($0.43 < n < 0.85$). In formulations with lowest levels of SA and $CaCO_3$, quasi-Fickian diffusion ($n < 0.43$) process prevailed. The study demonstrated that the *in situ* gelling formulations can be used as novel formulations with sustained drug release, improved bioavailability and thereby improve patient compliance.

INTRODUCTION: Salbutamol is a selective β_2-adrenoceptor stimulant and is given four times daily in a dose of 2.4 mg orally to maintain therapeutic blood level. The drug being safe with an average biological half life of 4.5 hr is suitable for preparation as an oral sustained release dosage form for 12 to 24 hr duration of action [1].

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It has been reported that the drug exhibits site specific absorption in the stomach and upper small intestine making it a potential candidate to be designed as gastroretentive dosage forms [2].

Gastroretention can be achieved by several approaches including formulating low density (floating) systems or high density systems, bio-adhesion to stomach mucosa, reducing motility of the GI tract by concomitant administration of drugs or pharmaceutical excipients and expanding dosage forms by swelling or unfolding to a large size which limits emptying of the dosage [3]. *In situ* gelling liquid systems which swell and form viscous cohesive gels with entrapped CO_2 bubbles

on contact with gastric fluid offer a novel option for floating gastroretentive drug delivery. In these systems an aqueous solution of polymers like alginate, gellan, pectin or chitosan containing drug, forms a gel upon contact with gastric fluid either due to pH change or ionic interaction. These systems can sustain drug release, improve bioavailability, reduce dosing frequency and improve patient acceptability [4, 5]. These systems have been investigated for the gastric delivery of amoxicillin [6], clarithromycin [7], metronidazole [8], acetohydroxamic acid [9], and levofloxacin hemihydrates [10] for eradication of *Helicobacter pylori* (*H. pylori*) and showed significant anti-*H.pylori* effect than the conventional dosage forms.

Alginate is a naturally occurring polyanionic polymer consisting of (1→4) linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues that are arranged in blocks composed of homopolymeric regions of M- and G- blocks interspersed with regions of alternating MG- blocks [11, 12]. The polymer is known to undergo ionotropic gelation and cross-linking with multivalent cations like calcium ions which is best illustrated by the so-called "egg-box" model [11]. Gelation of the polymer is mainly achieved by the exchange of sodium ions from the guluronic acids with the divalent cations[13].

The aim of the present study is to develop an effervescent floating liquid dosage form for salbutamol based on sodium alginate and HPMC K4M (viscosity inducer) with the advantage of sustained drug release, ease of administration and patient compliance. The system depends on ion activated gelation of sodium alginate in the presence of Ca^{2+} ions released from $CaCO_3$ in the acidic stomach fluid. The CO_2 generated from the reaction between $CaCO_3$ and simulated gastric fluid will be entrapped in the insoluble calcium alginate gel keeping it buoyant.

MATERIALS AND METHODS:

Materials:

Sodium alginate (AMIT Cellulose, Mumbai, India) was kindly supplied by Cadila Pharmaceuticals PLC, salbutamol sulfate raw material (Supriya Life science Limited, Mumbai, India) was generously supplied by Fews Pharmaceuticals PLC and the reference sample was obtained from Addis Pharmaceuticals Factory. The HPMC K4M was also a gift from Ethiopian Pharmaceuticals Manufacturing Sh. Co. Calcium carbonate (Bio-Lab limited, UK, London), sodium citrate (Uni-chem chemical reagents, India) and calcium chloride (SD fine-chem limited, Mumbai, India) were purchased from local suppliers. HCl used was of analytical grade.

Methods:

Preparation of *In Situ* Gelling Formulations:

Composition of the *in situ* gelling formulations is shown in **Table 1**. Accurately weighed solids were used to make the formulations as per the method described elsewhere [8, 14]. Accordingly, in about 30 ml of deionized water, HPMC K4M was allowed to hydrate overnight. Salbutamol sulfate was then dissolved in the HPMC K4M sol and $CaCO_3$ was added to it while stirring to facilitate dispersion. Sodium alginate solutions were prepared by adding the alginate to 60 ml of deionized water containing 0.25% w/v sodium citrate and 0.075% w/v calcium chloride and heating to 60 ^{0}C while stirring on a heating magnetic stirrer (AREX, VELP Scientifica, Italy). After cooling to below 40 ^{0}C, it was added to the HPMC solution while stirring to achieve uniform dispersion. Finally, the formulations were adjusted to volume, filled and stored in amber colored bottles until further tests were done.

Table 1: Composition of the *in situ* gelling formulations

Formulation Code	SS (%)	SA (%)	HPMC (%)	$CaCO_3$ (%)	Water
Effect of SA					
P1	0.192	0.25	0.5	1.00	q.s.
P2	0.192	1.75	0.5	1.00	q.s.
P3	0.192	3.25	0.5	1.00	q.s.
P4	0.192	4.75	0.5	1.00	q.s.
Effect of $CaCO_3$					
P5	0.192	1.75	0.5	0.25	q.s.
P6	0.192	1.75	0.5	1.75	q.s.
P7	0.192	1.75	0.5	2.50	q.s.

Determination of pH:

The pHs of all formulations were measured using a calibrated digital pH-meter (Wagtech; Jenway Ltd., London, UK) at room temperature and results were recorded as average of three measurements.

Determination of *In Vitro* Gelling Capacity:

To assess the *in vitro* gelling capacity, the method described by Rathod *et al* was employed [15]. Gelling

capacity was determined by placing 1 ml of each formulation into 5 ml of the gelation solution (0.1 N HCl) in a 15 ml borosilicate glass test tube maintained at 37±1 ^{0}C. Each formulation was added with a pipette; placing the pipette at the surface of liquid and slowly releasing the content. The *in vitro* gelling capacity of solution was evaluated and graded on the basis of stiffness of formed gel and the time taken for the gel to dissolve.

Determination of Viscosity:

Viscosity of the prepared *in situ* gelling formulations was determined using a rotational viscometer (VISCOSTAR *plus* L, Kinematica, AG; Switzerland). Viscosity was measured at different angular velocities (from 20 to 100 rpm) using spindle number 2 at room temperature. The hierarchy of the angular velocity was reversed (100 to 20 rpm). The average of the two readings was used to calculate the viscosity. Viscosity measurement for each formulation was done in triplicate [16].

***In Vitro* Floating Study:**

The *in vitro* floating study was determined with minor modification of the method used by Rajinikanth *et al* using USP dissolution apparatus II (ERWEKA DT 600HH, Germany) having 500 ml of simulated gastric fluid (0.1 N HCl) maintained at 37±1 ^{0}C with a paddle speed of 50 rpm[6]. Ten milliliters of the prepared *in situ* gelling formulations were withdrawn with disposable syringe (with removed tip) and added into the dissolution vessel containing simulated gastric fluid. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the dissolution medium surface (duration of floating) were recorded.

Construction of Calibration Curve:

Absorbance readings of serial dilutions (10-100 µg/ml) of salbutamol stock solution were taken using a single beam UV-Vis spectrophotometer at a λ_{max} of 276 nm (CECIL 1021, CECIL Instruments, England). The procedure was done in triplicate and calibration curve was plotted. The linear regression equation obtained was Y = 0.0069X + 0.003 with R^2 value of 1.000; where Y is the absorbance and X is concentration of salbutamol in µg/ml.

***In Vitro* Drug Release Study:**

Dissolution study was carried out by slightly modifying the methods reported by Miyazaki *et al* and Al-Ajeeli using USP paddle apparatus [17, 18]. 20 ml of each formulation equivalent to 32 mg salbutamol was measured using a disposable syringe (without the needle and its front tip cut off) and added to the dissolution medium (0.1N HCl, 500 ml at 37±1 ^{0}C). The paddle was rotated at 50 rpm; a speed slow enough to avoid breaking of gels and able to maintain the mild agitation conditions believed to exist *in vivo*. Ten milliliter samples were withdrawn at 30 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr with immediate replacement of equal volume of the fresh medium preheated to 37±1^{0}C. Absorbances of filtered samples were measured using single beam UV-Vis spectrophotometer at λ_{max} of 276 nm. The results were expressed as salbutamol cumulative percent released (CPR).

Analysis of Drug Release Kinetics:

To describe the kinetics of salbutamol release from the alginate gels, release data were fitted into zero order (Eq. 1), first order (Eq. 2), Higuchi (Eq. 3) and Hixson-Crowell Cube Root (Eq. 4) release models. The models were compared with respect to the correlation coefficients of the best fit straight lines[19].

$$Q = Q_o - k_1 t \qquad \text{Eq. (1)}$$

$$\log Q = \log Q_o - {k_2 t}/{2.303} \qquad \text{Eq. (2)}$$

$${M_t}/{M_o} = k_3 t^{1/2} \qquad \text{Eq. (3)}$$

$$Q^{1/3} = Q_o^{1/3} - k_4 t \qquad \text{Eq. (4)}$$

where Q represents amount of drug remaining at time t; Q_o represents the amount of drug initially present in dosage form; M_t is the amount of drug released at time t; M_o is the total amount of drug in the gels; M_t/M_o stands for fraction of drug released at time t; k_1, k_2, k_3, and k_4 represent rate constants for zero order, first order, Higuchi and Hixson-Crowell Cube Root rate equations respectively.

Drug release data were also fitted into Korsmeyer-Peppas power equation (Eq. 5) in order to find out the drug release mechanism:

$$M_t / M_o = kt^n \quad \text{Eq. (5)}$$

where, M_t is the amount of drug released at time t; M_o is the total amount of drug in the gels; M_t/M_o is the fraction of drug released in time t, k is constant, and n represents the release exponent indicative of mechanism of drug release [19].

RESULTS AND DISCUSSION:

pH of Formulations:

The formulations possessed satisfactory pH value ranging from 8.03 to 8.54 (**Table 2**) which is suitable to maintain the formulations in a liquid state. Aqueous solutions of sodium alginate are most stable at pH range of 4–10. Below pH 3, alginic acid is precipitated from the alginate solution making the formulation unsightly containing gel and liquid phases [20].

Gelling Capacity of Formulations:

As a prerequisite, an oral *in situ* gelling gastroretentive formulation should undergo rapid sol to gel transition when it comes in contact with the gastric fluid. Moreover, to facilitate sustained drug release, the *in situ* formed gel should preserve its integrity without dissolving for a prolonged period of time. In all the formulations, sol-to-gel transition occurred instantaneously at the formulation/simulated gastric fluid interface as the formulations were dropped from pipette. This instantaneous surface gelation formed an enclosing membrane which entrapped the remaining liquid formulation at the center and the gel layer expanded to the center apparently due to slow diffusion of H^+ and Ca^{2+} ions [21]. In line with this effect, during preliminary tests, the gels tend to ooze when pierced in less than 1 hr of gelation and at the end of the test period the gels appeared solid throughout their dimensions.

Similar results were reported by Zatz and Woodford for SA, gelatin and carrageenan *in situ* gelling formulations [22]. However, though gelation occurred instantaneously, the nature of the gels formed was dependent upon the polymer and $CaCO_3$ concentration. Low sodium alginate concentration (P1) formed weak gels (**Table 2**) which would not be able to withstand peristaltic waves of the GI tract, and might be propelled to the intestine with stomach contents. P1 could not last longer than 10 hr, even during this period it appeared very weak gel full of bubbles. P2 showed an intermediate gelling capacity, with stiffness lower than P3 and P4. Therefore, lower concentration of sodium alginate as in P1 could be of no value for sustained and site specific release of drugs such as salbutamol. The observed increase in gel strength with increased SA concentration is presumably due to increased polymer chain interaction[17].

TABLE 2: pH AND GELLING CAPACITY OF THE *IN SITU* GELLING FORMULATIONS

Formulation Code	Gelling Capacity*	pH
P1	+	8.54
P2	++	8.39
P3	+++	8.23
P4	+++	8.22
P5	++	8.03
P6	+++	8.27
P7	+++	8.27

* + = gelation immediate (< 10 s), weak gels dissolve after few hours (6 hr)

++ = gelation immediate (< 10 s), stiff gels remaining for 12 hr

+++ = gelation immediate (< 10 s), more stiff gels remaining for more than 24 hr

At lower $CaCO_3$ concentration, the gels did not go beyond 12 hr because at the $CaCO_3$ levels used, the available sodium alginate chains might not be sufficiently cross linked. In other words, the formed gels might not be of pure calcium-alginate gels which were reported elsewhere, to be stronger than the alginic acid gels. Through time, the Ca^{2+} ions may even be exchanged with the H^+ ions of the medium (0.1N HCl) leading to less attraction between the COO^- and Ca^{2+} creating weaker alginate gels. Bajpai and Sharma reported that treatment of calcium-alginate beads with 0.1N HCl for longer time resulted in gels which took short duration to disintegrate and dissolve [23].

Rheological Property of Formulations:

Viscosity of *in situ* gelling formulations should allow easy administration or swallowing as a liquid which would undergo rapid sol-to-gel transformation in the stomach due to acidic pH and

released cations. All the formulations showed pseudoplastic rheology as it was evident from their shear thinning behavior with increased angular velocity. Such type of flow is a characteristic feature of polymeric dispersions and advantageous in that it allows easy dispersion upon gentle shaking. Among the first four formulations, the shear thinning behavior was observed in pronounced manner among the formulations with higher sodium alginate concentration which was in agreement with the work of Miyazaki *et al* [24].

As it can be seen in **Fig.1**, viscosity of formulations at different shear rates was significantly ($P < 0.05$) affected by the concentration of sodium alginate. Higher polymer concentrations increase cross-linking density (chain interaction) between polymer chains and thus viscosity as also noted by Kesavan *et al* [16].

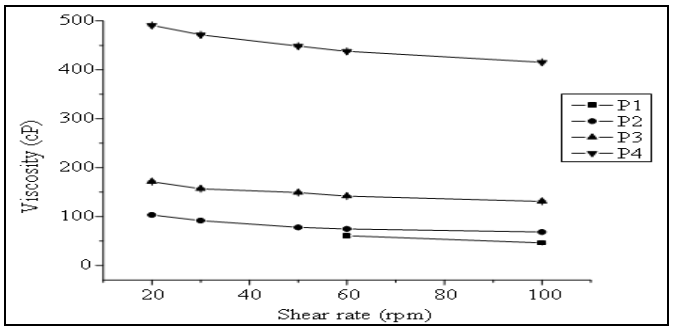

FIG.1: EFFECT OF CONCENTRATION OF SODIUM ALGINATE ON VISCOSITY OF *IN SITU* GELLING FORMULATIONS (DATA POINTS INDICATE MEAN AND ERROR BARS INDICATE STANDARD DEVIATION, N = 3).

Fig.2 reveals that concentration of $CaCO_3$ also had similar effect as polymer concentration on viscosity. Being an insoluble solid, $CaCO_3$ brought a significant increase in viscosity of the *in situ* gelling formulations ($P = 0.0047$ at 0.05 significance level) [15, 25, 26].

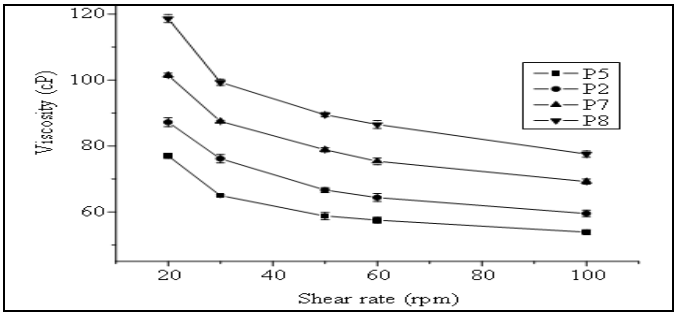

FIG.2: EFFECT OF CONCENTRATION OF $CaCO_3$ ON VISCOSITY OF *IN SITU* GELLING FORMULATIONS (DATA POINTS INDICATE MEAN AND ERROR BARS INDICATE STANDARD DEVIATION, N = 3).

In Vitro Floating Capacity:

Floating characteristics of prepared formulations were assessed in simulated gastric fluid (0.1 N HCl). All the formulations except P1 remained floating on the surface of the medium for at least 12 hr (**Table 3**). This indicates that the formulations could provide a sustained delivery of salbutamol to the absorption window for more than 12 hr as long as the gel was not depleted of the drug. P1, on the other hand, lost its integrity after 6 hr leaving bubbly remnant which disappeared after the 10th hr. This could indicate that the low SA concentration was not capable of withstanding the pressure developed by CO_2 released by the effervescence of $CaCO_3$. Therefore, higher polymer concentrations imparted extra strength to the gels to remain buoyant at least for 12 hr [26].

Formulations P5-P7 with fixed level of sodium alginate showed extended floating duration (> 12 hr) despite the changing $CaCO_3$ level suggesting that the amounts of $CaCO_3$ used were sufficient to induce buoyancy and the SA level used was sufficient to retain the released CO_2, thus, to maintain the low density.

TABLE 3: *IN VITRO* FLOATING CHARACTERISTICS OF *IN SITU* GELLING FORMULATIONS

Formulation Code	Floating Lag time (sec)	Floating Duration (hr)
P1	127	10
P2	40	> 12
P3	36	> 12
P4	31	> 12
P5	114	> 12
P6	39	> 12
P7	27	> 12

Regarding floating lag time, higher polymer concentrations shorten the time taken to float completely over the surface of the dissolution medium in agreement with other reports [7, 26]. This may be due to the higher cross-linking density at higher polymer concentrations which could effectively trap the released CO_2 bubbles so that density of the gel is reduced rapidly to induce buoyancy. Formulations (P2-P4) float to the surface after a very short lag time (less than a min). However; formulation P1, with the lowest sodium alginate concentration, took relatively longer (greater than 2 min). Similarly, $CaCO_3$

concentration was found to have an effect on floating lag time where the Ca^{2+} ions and CO_2 bubbles released in the acidic medium due to the effervescence of $CaCO_3$ might play role. The Ca^{2+} ions can crosslink the sodium alginate chains and the CO_2 may be retained in the cross linked gel barrier to make the gel buoyant. P5, the formulation with the lowest level of $CaCO_3$, took longer time to float over the surface of the medium. This might be attributed to the low concentration of CO_2 that could not sufficiently reduce the density of the formed gel. However, increasing concentrations of $CaCO_3$ showed a corresponding reduction of floating lag time [7, 26]. The formulations with longer floating lag time may be rapidly emptied from stomach. If so, the goal of attaining maximum bioavailability cannot be achieved as the drug salbutamol will reach distal parts of the intestine where it is minimally absorbed.

***In Vitro* Drug Release:**

As can be seen from **Fig.3** and **4**, all the formulations showed significant burst release where approximately, 41-61% of salbutamol was released within the first hr. This burst release might be attributed to the dissolved drug present at the surface of the formed gel that could have been released immediately upon contact with the 0.1N HCl. In addition to this, some lag time is required for the release of Ca^{2+} ions from $CaCO_3$ and cross linking of the guluronate residues of sodium alginate which plays a major role in the formation of barrier gel. The release profiles also depicted that all formulations release 60% or more of salbutamol within the first two hr and the remaining amount released at a steady rate that declines with time till the end of the dissolution study.

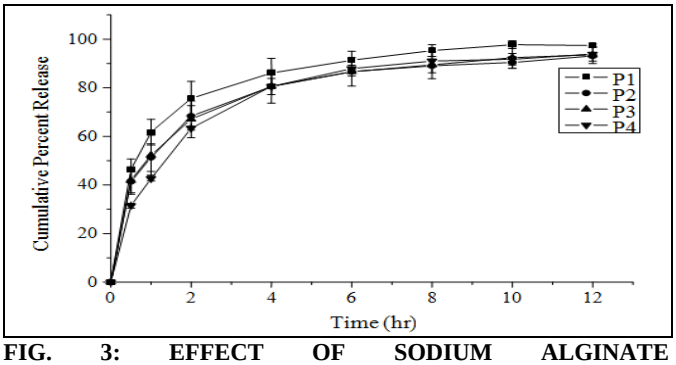

FIG. 3: EFFECT OF SODIUM ALGINATE CONCENTRATION ON RELEASE OF SALBUTAMOL (N = 3, ERROR BARS INDICATE SD)

Cohen *et al* and Balasubramaniam *et al* suggested that *in situ* gelling formulations are already hydrated systems based on aqueous vehicle, which facilitate rapid diffusion of the drug (soluble) across the gel barrier [27, 28]. But, when the formulations come in contact with the gelation solution and gels are formed, a prehydrated matrix is formed in which hydration and water penetration no longer limit drug release leading to an apparent diffusion-controlled release. In other studies, it was noted that as sodium alginate is converted to calcium alginate, the gel will shrink accompanied by loss of water due to increased cross-linking [29, 30]. This shrinkage and water loss will result in drug release retardation making the second phase of the release profile showing a steady rate.

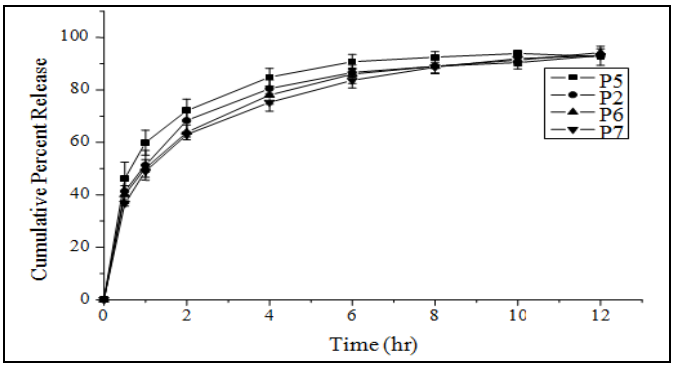

FIG.4: EFFECT OF $CaCO_3$ CONCENTRATION ON RELEASE OF SALBUTAMOL (N = 3, ERROR BARS INDICATE SD).

Increasing concentration of SA from 0.25 to 4.75% (**Fig. 3**) resulted in the reduction of salbutamol release. Higher polymer concentration levels reduced the release rate presumably due to the higher polymer density formed that could serve as an effective barrier across which the drug had to diffuse. Though higher SA contents resulted in slower release of salbutamol compared to the formulation with the lowest level of SA, a significant difference in drug release was not apparent among the formulations containing higher levels of the polymer. Similar findings have been reported elsewhere.

Miyazaki *et al* reported that release profiles of theophylline from 1.5 and 2% SA *in situ* gelling formulations were not significantly different but a 1% formulation showed a higher release rate compared to the two [17]. Similar relationships have been shown for theophylline preparations

containing SA and other similar polymers by Zatz and Woodford [22]. They indicated that 0.5% SA brought appreciable release retardation; however, further increment of polymer concentration to 1 and 3% reduced the release rate only slightly.

Marginal effect of polymer concentration on release rate of drugs was also demonstrated for other related polymers such as that done by Miyazaki *et al* for gellan based formulations of theophylline. Gellan is known to undergo ionotropic gelation like SA[31]. They noted insignificant difference in release among three concentrations of gellan. They suggested that the reason for this phenomenon is that gellan solutions formed rigid gels at acidic pH which brought about marked release retardation on which increased polymer concentration did not show significant effect. In another study, Verma and Pandit found insignificant effect of gellan concentration on drug release which they associated with inadequate availability of cross-linking agents for the higher polymer concentration [32]. This reason could also apply in our study where fixed amount of cross-linking agent ($CaCO_3$) was used at different levels of SA.

The effect of concentration of the cross-linking agent, $CaCO_3$, on the release of salbutamol is shown in **Fig.4.** As it can be observed, only the profile of P5 is clearly separable from the other three which appeared to be overlapping. This overlapping profile may be attributed to the fact that at a fixed SA concentration, the available sites for Ca^{2+} binding could be saturated; hence no extra strength of gels could be achieved on increasing $CaCO_3$.

The higher CO_2 formed might make the gels more porous with undesirable weakening effect on gel integrity. This finding is similar with that reported by Nagarwal *et al* where they found that increasing $CaCO_3$ concentration beyond 1.5% did not show appreciable release retardation compared to the formulations with lower concentration[5]. This relationship was also noted by Jagdale *et al* where they found faster drug release from pectin (a related polymer with SA) based beads containing 10% $CaCO_3$ than those containing 5% [33].

Drug Release Kinetics:

Correlation coefficients of the best fit linear equations for various release models *viz*., zero-order, first-order, Hixson Crowell's cube root, Korsmeyer-Peppas and Higuchi models suggest that salbutamol release from the alginate gels predominantly followed first order kinetics, as the values for log Q_0 – log Q vs. t (0.932-0.991) were, in all cases, higher than that for Q_o-Q vs. $t^{1/2}$ (0.909-0.960), Q_o-Q vs. t (0.794-0.873) and $Q^{1/3}$ vs. t (0.894-0.962). Similar kinetics of release was reported by Saeedi *et al* for sodium aginate tablets of theophylline (1:1) using $CaCl_2$ and $AlCl_3$ as cross-linking agents [34]. This kind of release kinetics is commonly observed in porous matrices containing soluble drugs where the calcium alginate gel matrix in the present study might become porous due to the escape of CO_2 bubbles from the matrix [35].

Mechanism of drug release from the gels was determined by the values of release exponent, n, calculated from the Korsmeyer-Peppas power law equation. Good correlation (0.935-0.988) was obtained with double logarithmic plots of fractional release as a function of time. The alginate formulations tend to form spherical matrix as also reported by Zatz and Woodford [22]. Fickian diffusional release (n = 0.43) and a Case-II relaxational (n = 0.85) release are the limits of the release process. The values calculated for the formulations fall in the range 0.389-0.670 which indicates that both Fickian and non-fickian (anomalous) processes might be operational in the release process. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient [25]. Case-II transport occurs due to polymer relaxation or swelling upon imbibition of water. Usually, drug release from polymeric systems follows Fickian diffusion process but in case of systems containing swellable polymers such as SA and HPMC, other processes like relaxation of polymer chains, imbibition of water causing polymer swelling and considerable volume expansion may take place [5, 36].

Two of the formulations with the lowest polymer and cross-linker concentrations yielded values less than 0.43 and the rest yielded greater values. Formulations with lower concentration of SA and

$CaCO_3$ that yielded values less than 0.43 may indicate that salbutamol was released from the gels by a quasi-Fickian type of diffusion. But at higher values of the two components, the process became more complex as the gels might have become more capable of imbibing large volume of dissolution medium which led to swelling and polymer chain relaxation.

CONCLUSION: The SA based *in situ* gelling formulations showed different properties based on their difference in composition. Except for the formulation with lowest level of SA, all systems preserved their integrity for the 12 hr study period. Furthermore, all these formulations, regardless of their composition, remained floating for the study period. Therefore, *in vivo*, the preparations are expected to remain in stomach long enough without being emptied into the intestine to provide a sustained release of salbutamol to be efficiently absorbed within its absorption window. The formulations showed satisfactory content uniformity and pH ensuring their safe use. The rheological study showed that the formulations possessed optimal viscosity and shear thinning behavior which can facilitate easy administration of the required dose. Nevertheless, the formulations possessed varying viscosity proportional to their SA and $CaCO_3$ content.

In vitro drug release study indicated that salbutamol release was sustained, the extent being dependent on the amount of SA and $CaCO_3$ used. Beyond certain values, however, change of concentration of SA and $CaCO_3$ did not show noticeable change in release profile. The effect of burst release was also influenced by levels of the two factors. Treatment of the release data with various kinetic models revealed that salbutamol release from the gels followed a first order kinetics and in most of the formulations (except those containing lowest SA and $CaCO_3$ levels) through anomalous transport mechanism. In general, results of this study indicate that sustained release and gastric retention of salbutamol can be achieved using SA as gel forming polymer and $CaCO_3$ as cross-linking and floating agent that can improve bioavailability of the drug, dosing frequency and hence patient compliance.

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