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In Situ Cross-Linked Matrix Tablets for Sustained Salbutamol Sulfate Release – Formulation Development by Statistical Optimization

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of the article

Abstract

Background. The use of natural polymers in designing of matrix tablets for sustained-release drug delivery systems has received much attention.
Objectives. The study involves the development and optimization of *in situ* cross-linked matrix tablets for sustained salbutamol sulfate release.
Material and Methods. *In situ* cross-linked matrix tablets of salbutamol sulfate were prepared by direct compression and optimized by response surface methodology based on 3^2 factorial design. The influence on sodium alginate and a calcium salt (calcium carbonate) amounts in salbutamol sulfate matrix tablets on the properties like drug release and hardness of salbutamol sulfate sustained release matrix tablets were analyzed by response surface plots and corresponding contour plots. Drug contents, weight variations, hardness, and *in vitro* drug release with release kinetic analysis of these newly developed matrix tablets were also investigated.
Results. All these *in situ* cross-linked salbutamol sulfate matrix tablets showed satisfactory drug contents, weight variations, hardness and prolonged sustained release of salbutamol sulfate over 6 h.
Conclusions. The developed salbutamol sulfate matrix tablets might be beneficial over the conventional tablets to decrease the dosing frequency and enhanced patient compliance (**Polim. Med. 2014, 44, 4, 221–230**).

Key words: salbutamol sulfate, matrix tablets, sustained release, optimization, factorial design.

Salbutamol sulfate is a direct acting sympathomimetic agent with a selective effect on β_2-adrenergic receptors, used in the treatment of acute as well as chronic asthma, bronchospasm and conditions with reversible airway obstruction, including chronic obstructive pulmonary disease (COPD) [1–3]. Salbutamol sulfate is readily absorbed from the gastrointestinal tract (GIT), when administered orally. Its plasma half-life is reported 4 to 6 h, and requires repeated administration of immediate release conventional tablets in a day in order to maintain the desired therapeutic level [4]. But repeated administration leads to tolerance to its bronchodilator effect [5]. Hence, sustained salbutamol sulphate release formulations like matrix tablets could be favourable to decrease the repeated administration frequency.

The sustained release formulations present some advantages like target-specificity, limiting fluctuation of plasma-drug level and side-effects, decreased repeated administration of dosage and enhanced patient compliance [6–8]. A variety of hydrophilic polymers have been employed to fabricate various types of matrix tablets for sustained drug release [9–12].

Recently, the use of natural polymers in designing sustained-release drug delivery systems has received much attention due to their excellent biocompatibility and biodegradability [13–22]. Among them, sodium alginate has been widely used as matrix in various sustained-release drug delivery systems [7, 23–24]. It is a hydrophilic anionic polysaccharide obtained from brown seaweeds [24]. It is a co-polymer of d-mannuronic acid and l-guluronic acid residues [25]. Sodium

alginate is reported form water-insoluble rigid calcium alginate gels by Ca^{2+} ion induced ionotropic gelation to encapsulate and release a wide variety of drugs [26–29]. However, easy solubility in water, substantial swelling and rapid erosion of sodium alginate matrix tablets are some of the limitations preventing it from being an ideal matrix material [30, 31]. When sodium alginate matrix tablets containing calcium salts come in contact with an acidic aqueous solution, *in situ* gelation of alginate takes place due to ionotropic interaction between sodium alginate and Ca^{2+} ions generated from the calcium salts [31]. In the previous literature, a few alginate-based matrix tablets were reported, which were formulated by direct compression of sodium alginate, drugs and calcium salts as sources of Ca^{2+} ions like calcium chloride, calcium gluconate or calcium acetate [30, 32–34]. In the current work, we attempted to develop sustained release sodium alginate-based matrix tablets of salbutamol sulphate by direct compression.

The conventional optimization of pharmaceutical formulations by altering a single variable at a time is a time-consuming and laborious method [29]. This method also requires a complete series of experiments for every variable (factor) of interest. Formulation optimization using various statistical experimental design methodologies has been widely applied in pharmaceutical formulation development. By designing a set of trial experimental runs, various statistical experimental designs reliably measure the effects of response variables by fitting appropriate mathematical models to the experimental data, conducting required statistical tests to determine optimal values of variables for the formulation of optimized products [35, 36]. Recently, factorial design has emerged as a statistical experimental design for formulation optimization design. Using this statistical optimization design, all factors involved in the formulation process can be studied in all possible combinations [26, 27]. The effect of factors and their interactions can also be analyzed through minimum experimentation [26–28]. In the current investigation, a two-factor and three-level (3^2) factorial design was applied to optimize matrix tablets for sustained salbutamol sulfate release as well as to investigate the effect of 2 independent process variables (factors) (i.e., sodium alginate and calcium carbonate amounts) on investigated responses (i.e., drug release and hardness of salbutamol sulfate matrix tablets).

Material and Methods

Material

Salbutamol sulfate (Albert-David Pvt. Ltd., India), sodium alginate (Central Drug House, India), calcium carbonate (Central Drug House, India), microcrystalline cellulose (PH 101) (B.S. Traders Pvt. Ltd., India), lactose (Merck Ltd., India) and magnesium stearate (Loba Chemie., India) were used. All other reagents and chemicals used were of analytical grade and commercially purchased.

Preparation of Salbutamol Sulfate Matrix Tablets

Matrix tablets of salbutamol sulfate were prepared by direct compression after proper mixing of salbutamol sulfate (20 mg) and suitable ratios of sodium alginate and calcium carbonate with others excipients. Salbutamol sulfate and all excipients were first passed through a sieve # 80 and uniformly mixed. Then, they were compressed using a single punch tablet punching machine (Cadmach Machinery Co. Pvt. Ltd., India) using 6 mm round and flat punches. The batch size was of 50 tablets.

Table 1. The formulation chart for all proposed trial formulations of salbutamol sulfate matrix tablets

Formulation codes	Salbutamol sulfate (mg)	Sodium alginate (mg) (A)	Calcium carbonate (mg) (B)	Lactose (mg)	MCC (mg)[a]	Mg-Stearate (mg)
F-1	20	125 (–1)	50 (–1)	70	20	10
F-2	20	125 (–1)	75 (0)	70	20	10
F-3	20	125 (–1)	100 (+1)	70	20	10
F-4	20	175 (0)	50 (–1)	70	20	10
F-5	20	175 (0)	75 (0)	70	20	10
F-6	20	175 (0)	100 (+1)	70	20	10
F-7	20	225 (+1)	50 (–1)	70	20	10
F-8	20	225 (+1)	75 (0)	70	20	10
F-9	20	225 (+1)	100 (+1)	70	20	10

[a] MCC = microcrystalline cellulose; A and B represent the main effects (factors); (+1) = higher level, (0) = medium level and (–1) = lower level.

Experimental Design

3^2 factorial design was employed for the formulation optimization of salbutamol sulfate matrix tablets using Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA). Sodium alginate (A) and calcium carbonate (B) amounts were selected as factors in this investigation, which were varied at low, medium and high levels. According to the trial proposal of 3^2 factorial design, different salbutamol sulfate matrix tablets were formulated. Cumulative drug release after 5 h (R_{5h}, %) and hardness (kg/cm^2) were investigated as responses. The matrix of the 3^2 factorial design including factors and responses are given in Table 2. The effects of factors on investigated responses (i.e., R_{5h} and hardness) were modeled using polynomial equations involving factors and their interactions by 3^2 factorial design [26, 27]: $Y = b_o + b_1A + b_2B + b_3AB + b_4A^2 + b_5B^2$; where Y is the response, while b_o is the intercept, b_1, b_2, b_3, b_4, b_5 and b_6 are regression coefficients; A and B are factors; AB is interaction between factors.

Determination of Drug Content

20 salbutamol sulfate matrix tablets from each batch were taken, weighed and crushed to powder form using pestle and mortar. Crushed tablet powders equivalent to 20 mg salbutamol sulfate was transferred into a 100 mL volumetric flask and the volume was made up to 100 mL with 0.1N HCl. To dissolve the powdered material, shaking was done and then, solutions were filtered using Whatmann® filter paper (No. 40). Absorbance values were measured using a UV-VIS spectrophotometer (Thermo Spectronic UV-1, USA) at 225 nm.

Weight Variation Determination

20 salbutamol sulfate matrix tablets were sampled from each batch and accurately weighed using an electronic analytical balance (Mettlar-Toledo). The weight variation (%) of these matrix tablets was measured using this formula [8]: weight variation (%) = standard deviation/mean weight × 100

Hardness Testing

To determine the hardness of salbutamol sulfate matrix tablets, Pfizer hardness tester was used. The tablets were first placed in between 2 jaws after adjusted the tester to zero. Force was applied until the breaking of tablet in to fragments and readings were noted.

In Vitro Drug Release Studies

In vitro salbutamol sulfate release from salbutamol sulfate matrix tablets was performed in basket type USP dissolution apparatus (Campbell Electronics, India). Salbutamol sulfate matrix tablets were placed into the basket containing 900 mL of 0.1N HCl (pH 1.2) as dissolution medium and dissolution study continued for first 2 h. After 2 h dissolution in 0.1N HCl, phosphate buffer (pH 7.4) was used as dissolution medium for next hours, which were maintained at 37 ± 0.5°C. The study was performed at 50 rpm. At specific time intervals, 5 mL aliquots were withdrawn and equivalent volume of fresh mediums were replaced. Samples were filtered using Whatmann® filter paper (No. 40) and then, absorbance values were measured using a UV-VIS spectrophotometer (Thermo Spectronic UV-1, USA) at 225 nm for determination of salbutamol sulfate.

Table 2. 3^2 factorial design and their observed response values in the formulation development of salbutamol sulfate matrix tablets

Formulation codes	Sodium alginate (mg) (A)	Calcium carbonate (mg) (B)	Responses	
			R_{5h} (%)[a,b]	Hardness (kg/cm^2)[b]
F-1	125 (–1)	50 (–1)	93.24 ± 4.42	3.80 ± 0.03
F-2	125 (–1)	75 (0)	85.96 ± 3.18	3.98 ± 0.07
F-3	125 (–1)	100 (+1)	83.65 ± 3.04	4.04 ± 0.05
F-4	175 (0)	50 (–1)	86.65 ± 3.52	3.88 ± 0.06
F-5	175 (0)	75 (0)	79.55 ± 3.16	4.11 ± 0.03
F-6	175 (0)	100 (+1)	75.66 ± 2.98	4.26 ± 0.06
F-7	225 (+1)	50 (–1)	85.59 ± 3.02	4.14 ± 0.08
F-8	225 (+1)	75 (0)	76.67 ± 2.81	4.37 ± 0.07
F-9	225 (+1)	100 (+1)	69.83 ± 2.42	4.54 ± 0.08

[a] R_{5h} (%) = cumulative drug release after 5 h; [b] mean ± S.D., n = 6; A and B represent the main effects (factors); (+1) = higher level, (0) = medium level and (–1) = lower level.

Kinetic Analysis of *in Vitro* Drug Release Data

To analyze the drug release mechanism of these salbutamol sulfate matrix tablets, the *in vitro* dissolution data were fitted to various important mathematical models [37]:

Zero-order Model: $F = K_0 t$,

First-order Model: $\ln (1-F) = - K_1 st\ t$,

Higuchi Model: $F = K_H t^{½}$,

Korsmeyer-Peppas Model: $F = K_P t^n$, where F represents the fraction of drug released in time t, K_0 is the zero-order release constant, K_1 is the first-order release constant, K_H is the Higuchi dissolution constant, K_P is the rate constant and n is the release exponent. Again, the Korsmeyer-Peppas model has been employed to distinguish between various release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (relaxation-controlled release). When, n is ≤ 0.5, it is Fickian release. The n value between 0.5 and 1.0 is defined as non-Fickian release. When, n is ≥ 1.0, it is case-II transport [37].

Statistical Analysis

Statistical optimization was performed using Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA). All other data was analyzed with simple statistics using BioStat version 2009 for Windows software, AnalystSoft Inc.

Results and Discussions

Optimization of Salbutamol Sulfate Matrix Tablets

Unadventurously, pharmaceutical formulators develop various pharmaceutical formulations by changing one factor at a time, which is laborious and lengthy [28]. On the other hand, optimization by means of statistical experimental design methodologies is a set of experiments that will generate mathematical models with conducting statistical tests to determine values of investigated factors to produce optimal quality products [27]. Currently, statistical optimization methodologies have been widely applied in the formulation development of various pharmaceutical formulations [26–29, 35, 36]. Among various statistical optimization methodologies, factorial designs are considered the most efficient in estimating the effects of various factors with minimum experimentation. In factorial designs, all factors are analysed in all possible combinations [38, 39]. A total 9 trial formulations of salbutamol sulfate matrix tablets were proposed by the 3^2 factorial design for 2 factors: amounts of sodium alginate (A) and calcium carbonate (B), and 2 responses: R_{5h} and hardness. In Table 2, an overview of the values of factors and observed responses are presented. The ANOVA results indicated that the investigated models were found significant (Table 3). The model equations were: R_{5h} (%) = 137.69 – – 0.27 A – 0.43 B + 1.23 × 10^{-3} AB + 7.48 × 10^{-4} A^2 + + 2.73 × 10^{-3} B^2 [R^2 = 0.9959; F-value = 145.21; p < 0.05], and hardness (kg/cm^2) = 3.67 – 6.93 × 10^{-3} A + 0.01 B + 3.20 × 10^{-5} AB + 2.46 × 10^{-3} A^2 – 6.93 × 10^{-5} B^2 [R^2 = 0.9966; F-value = 176.02; p < 0.05]

Simplified models by reducing non-significant terms (p > 0.05) [40] were: R_{5h} (%) = 137.69 – 0.27 A – 0.43

Table 3. Summary of ANOVA for response parameters

Source	Sum of square	d.f.[a]	Mean square	*F* value	*p*-Value prob > *F*
For R_{5h}(%)[b]					
Model	400.15	5	80.03	145.21	0.0009 (S)
A	157.70	1	157.70	286.12	0.0004 (S)
B	220.10	1	220.10	399.35	0.0003 (S)
AB	9.52	1	9.52	17.27	0.0253 (S)
A^2	6.99	1	6.99	12.69	0.0378 (S)
B^2	5.58	1	5.58	10.61	0.0472 (S)
For Hardness (kg/cm^2)					
Model	0.44	5	0.09	176.02	0.0007 (S)
A	0.25	1	0.25	500.59	0.0002 (S)
B	0.12	1	0.12	392.04	0.0003 (S)
AB	6.40 × 10^{-3}	1	6.40 × 10^{-3}	12.71	0.0377 (S)
A^2	7.60 × 10^{-3}	1	7.60 × 10^{-3}	15.10	0.0302 (S)
B^2	3.75 × 10^{-3}	1	3.75 × 10^{-3}	7.46	0.0719 (NS)

[a] d.f. indicates degree of freedom; [b]R_{5h} (%) = cumulative drug release after 5 h; A and B represent the main effects (factors) – the amounts of sodium alginate and calcium carbonate in mg, respectively; A^2 and B^2 are the quadratic effect; AB is the interaction effect; S and NS indicate significant and non significant, respectively.

$B + 1.23 \times 10^{-3}$ AB + 7.48×10^{-4} A^2 + 2.73×10^{-3} B^2, and Hardness (kg/cm^2) = $3.67 - 6.93 \times 10^{-3}$ A + 0.01 B + + 3.20×10^{-5} AB + 2.46×10^{-3} A^2

The effects of factors on responses were further clarified by response surface methodology, which is a widely applied approach in the formulation optimization [8, 28]. 3-dimensional response surface plots are especially helpful in learning about the main and interaction effects of factors, whereas 2-dimensional contour plots give visual representations of values of the response [8, 35]. Response surface plots (Fig. 1 and 2) and corresponding contour plots (Fig. 3 and 4) indicate the decreased values of R_{5h} and increased values of hardness with the increment of both factors investigated for the formulation optimization of salbutamol sulfate matrix tablets. To achieve optimized salbutamol sulfate matrix tablets, numerical optimization based on desirability approach was employed. Desirable ranges of R_{5h} and hardness values were restricted to $65 \leq R_{5h} \leq 70$ %, and $4.5 \leq$ hardness ≤ 5 kg/cm^2. The ranges of values of factors were restricted to $235 \leq A \leq 270$ mg and $120 \leq B \leq 140$ mg. The optimal values of responses were obtained by numerical analysis using the Design-Expert 8.0.6.1 software based on the criterion of desirability. The overlay plot indicating the region of optimal process variable settings was presented in Fig. 5. The selected optimal setting used for the optimized formulation were A= 262.93 mg and B = 134.57 mg. Optimized salbutamol sulfate matrix tablets (F-O) were prepared and evaluated for R_{5h} and

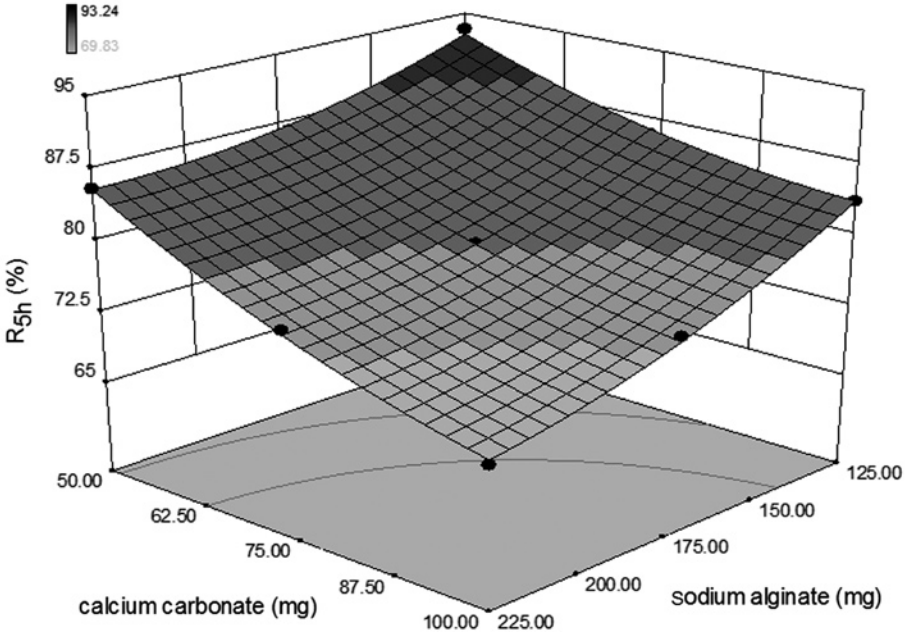

Fig. 1. Effect of amounts of sodium alginate and calcium carbonate on R5h (%), presented by response surface plot

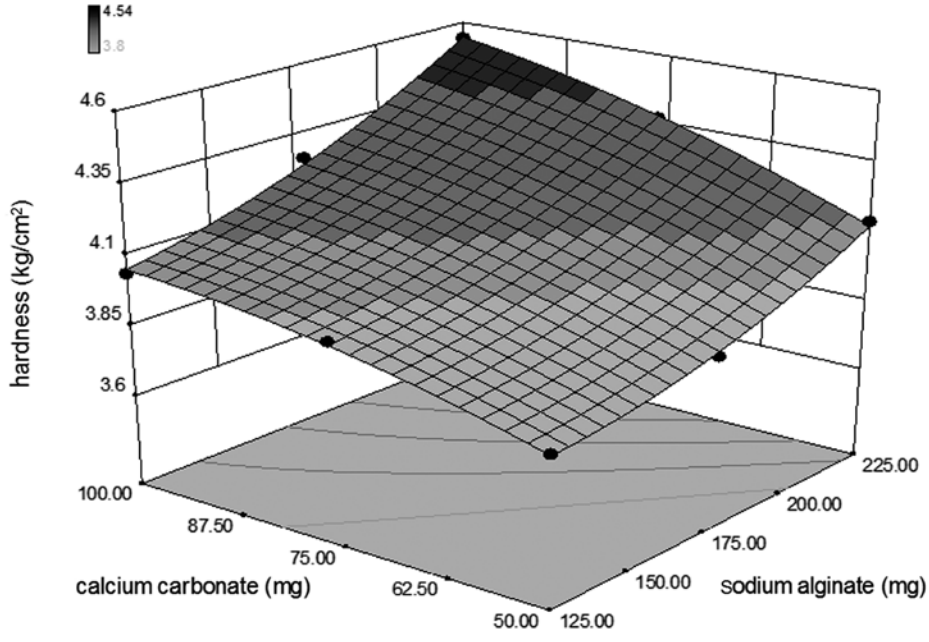

Fig. 2. Effect of amounts of sodium alginate and calcium carbonate on hardness (kg/cm^2), presented by response surface plot

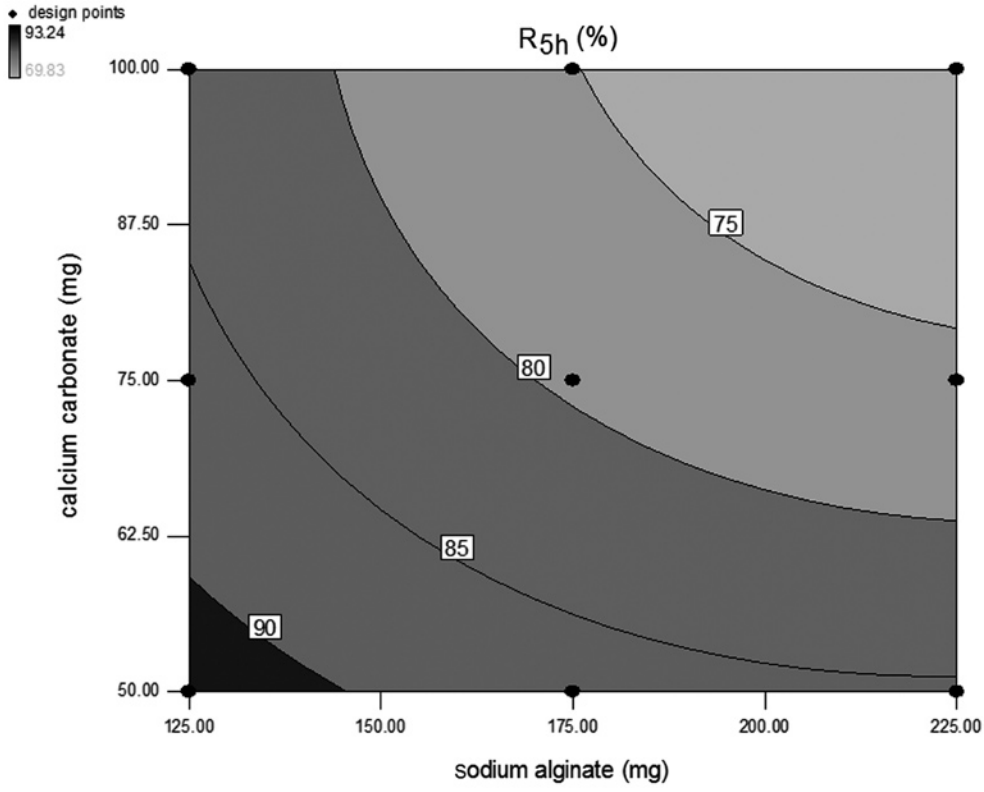

Fig. 3. Effect of amounts of sodium alginate and calcium carbonate on R5h (%), presented by contour plot

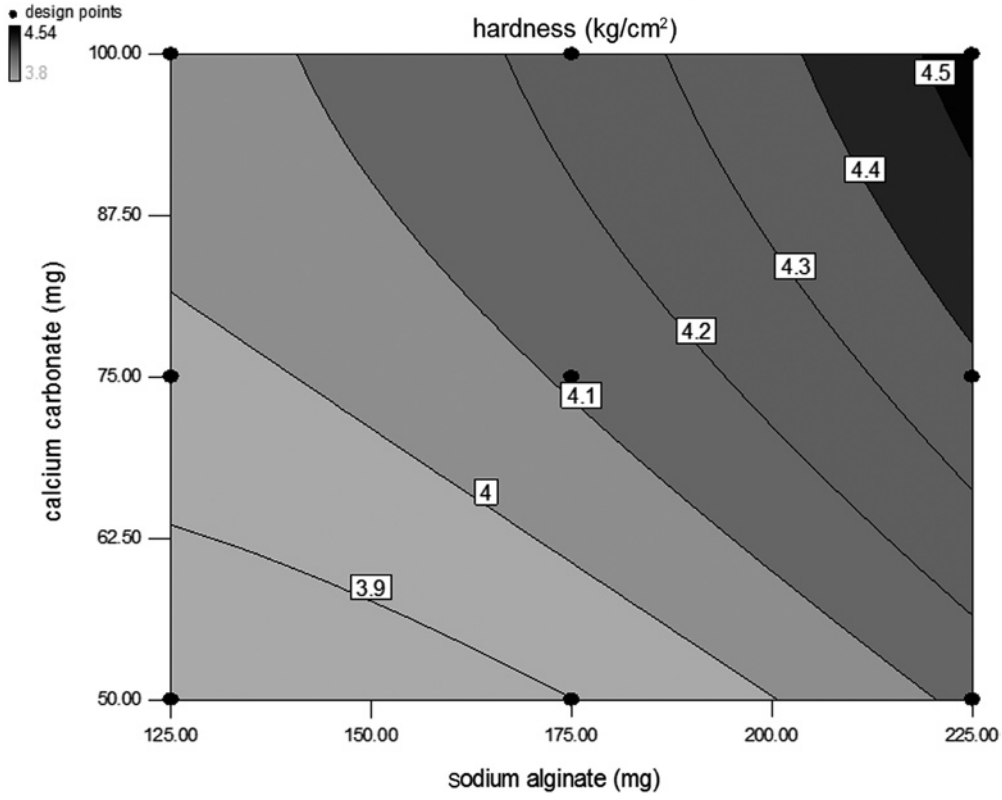

Fig. 4. Effect of amounts of sodium alginate and calcium carbonate on hardness (kg/cm^2), presented by contour plot

hardness. Predicted values obtained from generated mathematical models and actual values were presented in Table 4. Optimized matrix tablets (F-O) showed R_{5h} of 67.54 ± 2.42 %, and hardness of 4.85 ± 0.11 kg/cm^2 within small error-values (3.81 and – 2.80, respectively).

Drug Content and Weight Variation

Formulated salbutamol sulfate matrix tablets contained salbutamol sulfate within 96.48 ± 1.84 to 99.16 ± 0.92 (Table 5), indicating uniform drug content

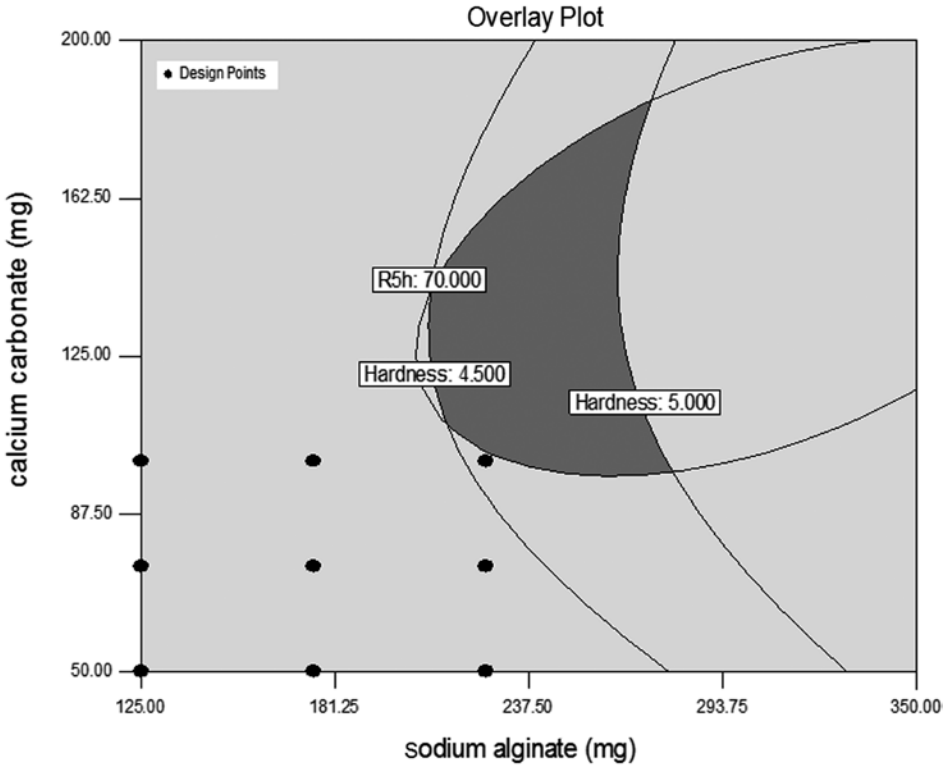

Fig. 5. Overlay plot showing the region of optimal process variable settings (dark area)

Table 4. Results of experiments to assure optimization capability

Code	Sodium alginate (mg) (A)	Calcium carbonate (mg) (B)	Responses	
			R_{5h}(%)[a]	Hardness (kg/cm^2)
F-O	262.93	134.57	actual values[b] 67.54 ± 2.42 predicted values 65.06	actual values[b] 4.85 ± 0.11 predicted values 4.99
% Error[c]	3.81	–2.80		

[a] R_{5h} (%) = cumulative drug release after 5 h; [b] Actual values = mean ± S.D., n = 6; [c]% error = [(actual value – predicted value)/predicted value] × 100; A and B represent the main effects (factors).

Table 5. Drug content and weight variation of salbutamol sulfate matrix tablets

Formulation codes	Drug content (%)[a]	Weight variation (%)[b]
F-1	98.12 ± 0.73	3.30 ± 0.09
F-2	96.48 ± 1.84	3.15 ± 0.28
F-3	98.06 ± 0.93	2.88 ± 0.17
F-4	97.37 ± 0.77	3.12 ± 0.22
F-5	98.11 ± 0.92	3.39 ± 0.25
F-6	99.02 ± 1.12	3.43 ± 0.23
F-7	97.33 ± 0.73	2.92 ± 0.19
F-8	96.49 ± 0.87	1.96 ± 0.09
F-9	99.16 ± 0.92	3.18 ± 0.18
F-O	98.53 ± 0.77	2.87 ± 0.20

[a] mean ± S.D., n = 20; [b] coefficient of weight variation (%) = standard deviation/mean weight × 100.

in these matrix tablets. The weight variation of these salbutamol sulfate tablets was varied from 1.96 ± 0.09 to 3.39 ± 0.25 % (Table 5). The results shows that none of the salbutamol sulfate tablets had deviated up to 5 %, which complied with the USP specifications [41]. The uniform salbutamol sulfate content and weight uniformity of these salbutamol sulfate matrix tablets indicate the uniform mixing of salbutamol sulfate with other ingredients used in formulation of matrix tablets.

Hardness

A force of about 4 kg/cm^2 is considered as the satisfactory hardness for tablets [42]. The hardness of all these salbutamol sulfate matrix tablets were within the range, 3.80 ± 0.03 to 4.85 ± 0.11 kg/cm^2 (Table 2 and Table 4) indicating their satisfactory hardness.

In Vitro Drug Release

All salbutamol sulfate matrix tablets displayed prolonged drug release over a period of 6 h (Fig. 6). Salbutamol sulfate release was found slower in the first 2 h at pH, 1.2. After that, it was found faster at pH, 7.4. The salbutamol sulfate release retardation from these tablet matrices might be due to the formation of *in situ* rigid gel of calcium alginate during dissolution through calcium ion-induced ionic gelation of alginate [7]. With

Table 6. Results of curve fitting of the *in vitro* salbutamol sulfate release data from different salbutamol sulfate matrix tablets

Formulation code	Correlation coefficient (R^2)	Release exponent (n)			
	Zero-order	First-order	Higuchi	Korsmeyer-Peppas	
F-1	0.996	0.863	0.870	0.995	0.96
F-2	0.992	0.869	0.856	0.990	0.95
F-3	0.997	0.823	0.873	0.992	0.95
F-4	0.997	0.889	0.883	0.991	0.89
F-5	0.997	0.916	0.877	0.995	0.93
F-6	0.992	0.864	0.857	0.978	0.99
F-7	0.995	0.907	0.867	0.993	0.94
F-8	0.998	0.894	0.889	0.998	0.90
F-9	0.997	0.924	0.877	0.992	0.97
F-O	0.998	0.908	0.873	0.997	0.96

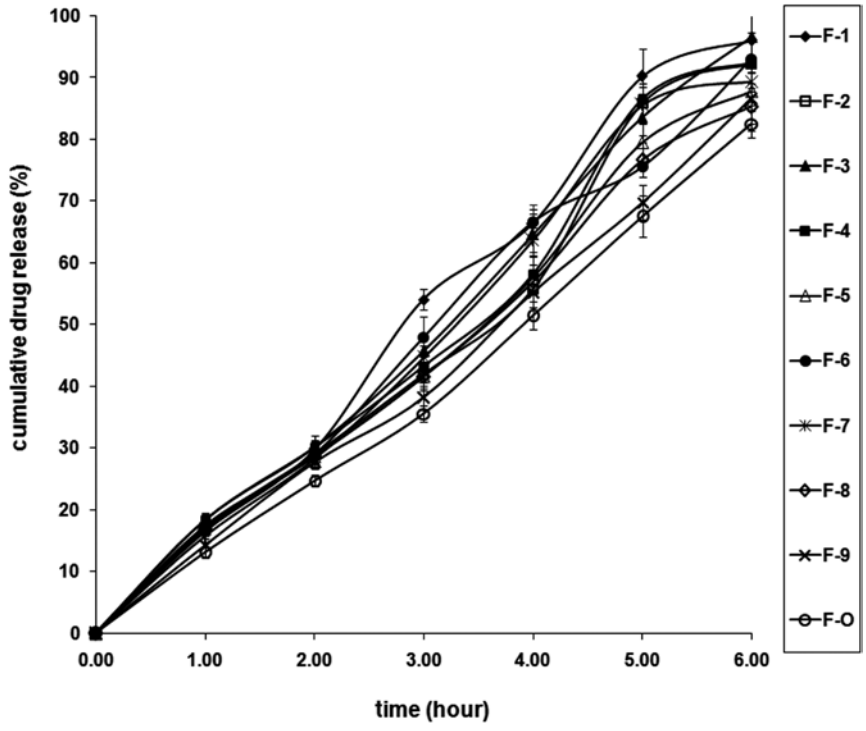

Fig. 6. *In vitro* drug release from various *in situ* cross-linked salbutamol sulfate matrix tablets (F-1 to F-O). Values are represented as (mean ± S.D., n = 6)

the increments of sodium alginate and calcium carbonate, availabilities of cross-linking sites and cross-linker should be increased. The viscosity increment due to increasing sodium alginate amount could produce highly viscous gels, when it comes in contact with aqueous dissolution medium. This could impede the drug release. On the other hand, increasing calcium carbonate amount could produce a high degree of *in situ* cross-linking due to an electrostatic ionic interaction between positively charged calcium ions released from calcium carbonate and negatively charged alginate ions. This phenomenon could slow the drug release from highly cross-linked alginate matrices.

The results of the curve fitting into various important mathematical models are given in Table 6. The drug release from salbutamol sulfate matrix tablets was found to follow the zero-order model (R^2 = 0.992 to 0.998) and Korsmeyer-Peppas model (R^2 = 0.990 to 0.998) over 6 h. The values of release exponent (n) determined ranged from 0.89 to 0.99 indicating anomalous (non-Fickian) diffusion mechanism, which demonstrated both diffusion controlled and swelling controlled drug release. The release exponent nearer to 1 indicates swelling controlled drug release is prominent.

In situ cross-linked matrix tablets for sustained salbutamol sulfate release were developed by statistical optimization. The amounts of sodium alginate and calcium carbonate on salbutamol sulfate release and hardness of matrix tablet were analyzed and optimized based on 3^2 factorial design. The response surface plots and corresponding contour plots indicated the decreased values of R_{6h} and increased values of hardness with the increment of amounts of sodium alginate and calcium carbonate in salbutamol sulfate matrix tablets. These developed optimized salbutamol sulfate matrix tablets showed prolonged sustained release of salbutamol sulfate over 6 h and might be advantageous over the conventional salbutamol sulfate tablets to reduce the dosing frequency with improved patient compliance.

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