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FORMULATION AND EVALUATION OF SALBUTAMOL SULPHATE FLOATING MICROSPHERES

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Abstract:

Salbutamol is a beta-2 adrenergic receptor agonist used to treat asthma, bronchitis, COPD, as well as prevent exercise induced bronchospasms the present work is formulation of salbutamol sulphate floating microspheres by using xanthan gum, and guar gum. All the formulations were subjected for preformulation evaluation. Results of preformulation studies, FTIR, SEM, particle size and size distribution, % yield, drug content, buoyancy time, entrapment efficiency, in vitro dissolution, and release kinetics. The FTIR Spectra revealed that, there was no interaction between polymers and Salbutamol sulphate. On the basis of release data of Salbutamol sulphate formulation F8 showed a good controlled release profile with maximum entrapment efficiency because of optimum polymer concentration i.e., 1:1.5:1.5 ratio (Xanthum gum and guar gum) with sodium alginate than other drug: polymer ratios. The invitro dissolution data for best formulation F8 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F8 shows zero order drug release with Super case II transport mechanism.

***Keywords**: Salbutamol sulphate, xanthan gum, sodium alginate, karaya gum, FTIR, SEM*

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INTRODUCTION:

The basic goal of novel drug delivery system (Remington, 2001) is to achieve a steady state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. These dosage forms have been found to have serious limitations in terms of higher doses required lower effectiveness, toxicity and adverse effects [1]. NDDS are being developed rapidly, so as to overcome the limitations of conventional drug delivery. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature) [2]. In this present investigation it was proposed to formulate Salbutamol sulphate floating microspheres using polymers sodium alginate and different polymers like xanthan gum, karaya gum and sodium bicarbonate for buoyant and controlled delivery, and also to compare the release kinetics of floating microspheres of Salbutamol sulphate.

DRUG PROFILE: 1) Salbutamol sulphate: Description: Salbutamol is a short-acting, selective beta2-adrenergic receptor agonist used in the treatment of asthma and COPD[3]. It is 29 times more selective for beta2 receptors than beta1 receptors giving it higher specificity for pulmonary beta receptors versus beta1-adrenergic receptors located in the heart [19]. Salbutamol is formulated as a racemic mixture of the R- and S-isomers[4]. The R-isomer has 150 times greater affinity for the beta2-receptor than the S-isomer and the Sisomer has been associated with toxicity[20].

EXCIPIENT PROFILE: Xanthan Gum: It occurs as a cream or white colored odorless free flowing fine powder. Karaya Gum: Sodium alginate occurs as a white or buff powder which is odourless and tasteless. Sodium alginate: Sodium alginate consists of mainly of the sodium salt of alginic acid which is a mixture of polyuronic acids [(C6H8O6) n] composed of β-D-mannuronic acid and residue linked so that the carboxyl group of each unit is free while the aldehyde group is shielded by a glycosidic linkage[6]. Sodium Bicarbonate: Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. Calcium Chloride: Calcium chloride is an ionic compound of calcium and chlorine. It is highly soluble in water and it is deliquescent.

METHODOLOGY:

List of chemicals used with grade and supplier

Sl. no.	Materials used	Manufacturer
1	Salbutamol sulphate	LEE Pharma Pvt Ltd, Hyderabad
2	Sodium alginate	S D fine chemical Ltd, Mumbai
3	Xanthan gum	Loba chemie Pvt. Ltd., Mumbai
4	Guar gum	S D fine chemical Ltd, Mumbai
5	Calcium chloride	Loba chemie Pvt. Ltd. Mumbai
6	NaHCO3	S D fine chemical Ltd, Mumbai
7	Hydrochloric acid	Loba chemie Pvt. Ltd. Mumbai

PREFORMULATION STUDIES:

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients [21]. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

FORMULATION:

Formulation design for Salbutamol sulphate Floating Microspheres using different ratios of drug & polymers.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Salbutamol sulphate	200	200	200	200	200	200	200	200
Sodium Alginate	250	250	250	250	250	250	250	250
Xanthan gum	300	500	-	-	200	100	300	300
Guar gum	-	-	300	500	200	300	100	300
Drug: polymer	1:1.5	1:2.5	1:1.5	1:2.5	1:1:1	1:0.5:1.5	1:1.5:0.5	1:1.5:1.5
NaHCO3(mg)	30	30	30	30	30	30	30	30
Calcium chloride (%)	1	1	1	1	1	1	1	1

Preparation of Floating microspheres of Salbutamol sulphate:

Method used – **orifice ionic gelation method**: The floating microspheres containing Salbutamol sulphate were prepared by orifice ionic gelation technique [7]. Sodium alginate along with in combination with different natural polymers and the gas forming agent sodium bicarbonate were dispersed in the purified water to form a homogeneous polymer mixture [17]. The drug, Salbutamol sulphate was added to the polymer dispersion and mixed thoroughly on a magnetic stirrer to form a homogeneous dispersion. The gelation medium was prepared by dissolving calcium chloride in distilled water. The homogenous alginate solution was extruded using 21G syringe needle into the gelation medium[8]. The distance between the edge of the needle and surface of gelation medium was about 10cms. The gel microspheres formed were left in the solution with gentle stirring for 30 min at room temperature to improve mechanic strength[18]. After that, microsphere was collected and washed with distilled water twice, dried at room temperature for 24 hr and stored in desiccators.

Evaluation of Salbutamol Sulphate Floating Microspheres:

Surface morphology (SEM) Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface[9]. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan)[17]. Dry Salbutamol sulphate gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Salbutamol sulphate microspheres were taken by random scanning of the stub.

Drug Entrapment Efficiency: 75mg of prepared floating alginate beads of Salbutamol sulphate were dissolved in 50 ml of 6.8 pH phosphate buffer and the drug content was analyzed at 276 nm using a UV/visible spectrophotometer (PG Instruments T60)[10]. Encapsulation efficiency was calculated as the percentage (w/w) of the theoretical drug content.

EE (%) = Actual Drug Content/ Theoretical Drug Content X 100

***In-vitro* dissolution studies:**

Procedure for *In-vitro* dissolution study: The release rate of Salbutamol sulphate Microspheres was determined by employing USP apparatus II (Paddle method) [22]. The dissolution test was performed. using 900 ml 6.8 pH phosphate buffer, in 37 ±0.5°C at 50 rpm. Salbutamol sulphate microspheres equivalent to 25 mg of Salbutamol sulphate was used for the study [11]. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for upto 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 276 nm[12]. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism.

RESULTS: Solubility study

Table 4: Solubility studies of salbutamol sulphate:

Solvent	Solubility (µg/ml)
0.1N HCl	0.226±0.025
6.8 pH buffer	0.738±0.047
7.4 pH buffer	0.589±0.082
Water	0.067±0.017

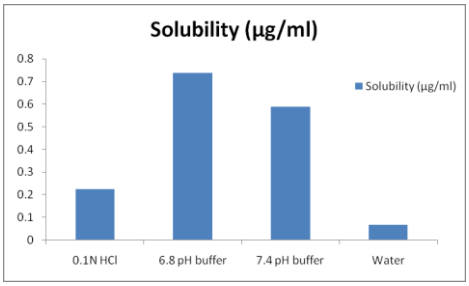

Fig1: Solubility studies of salbutamol sulphate

Discussion: The solubility of salbutamol sulphate was occurs more on 6.8 pHphosphate buffer with compare of 7.4 pH phosphate buffer and 0.1 N HCl solution.

Melting point: The melting point of salbutamol sulphate was found to be 180 ºC

Determination of λ_{max}

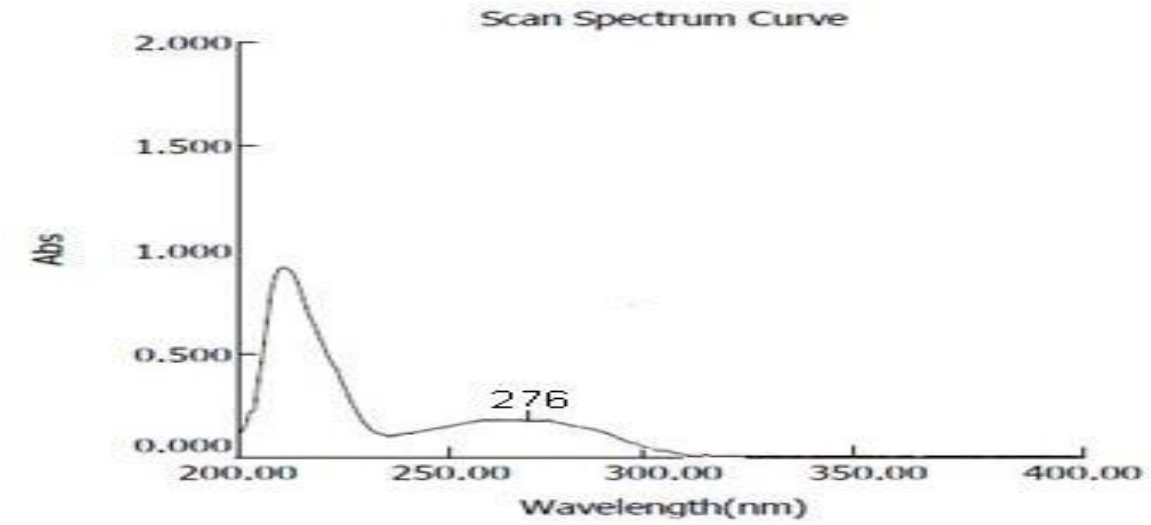

Fig2: λmax of Salbutamol sulphate in 6.8 pH buffer (10µg/ml)

Discussion: The maximum absorbance was found to be at 276 nm.

Calibration curve of Salbutamol sulphate at λmax of 276 nm

Table 5: Standard calibration data of Salbutamol sulphate in 0.1N HCL

Concentration(µg/ml)	Absorbance
0	0
5	0.124±0.025
10	0.258±0.040
15	0.384±0.017
20	0.492±0.024
25	0.616±0.019
30	0.728±0.012

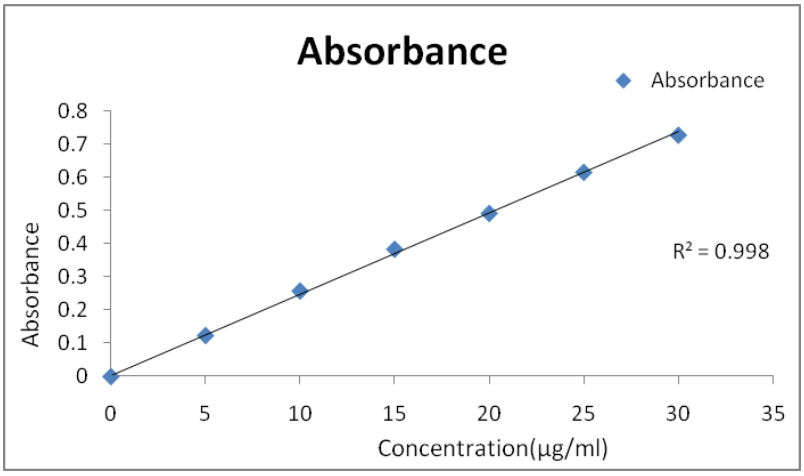

Fig3: Standard calibration curve of Salbutamol sulphate in 0.1N HCL

Table 6: Standard calibration data of Salbutamol sulphate in 6.8 pH buffer

Concentration(µg/ml)	Absorbance
0	0
5	0.168±0.025
10	0.315±0.027
15	0.497±0.013
20	0.656±0.019
25	0.798±0.020
30	0.955±0.017

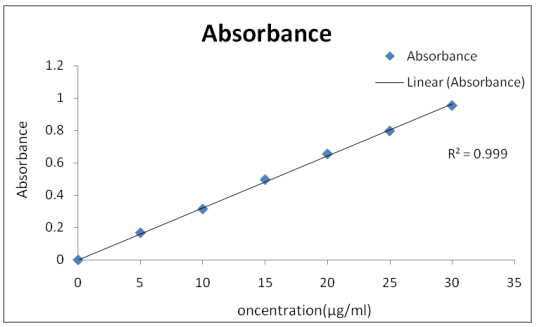

Fig4: Standard calibration curve of Salbutamol sulphate in 6.8 pH buffer

DRUG –POLYMER COMPATIBILITY STUDIES BY FTIR:

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). Infrared (IR) spectra were obtained on a (2 mg sample in 200 mg KBr) [16]. The scanning range was 400 to 4000 cm-1 and the resolution was 1 cm^{-1}. FTIR absorption spectra of pure drug and all the polymers used like HPMC, SCMC, CP, PVP, EC and the combination of drug and polymers were shows no significant interaction between drug and polymers[13]. The spectra obtained were shown in the Figure 5-11.

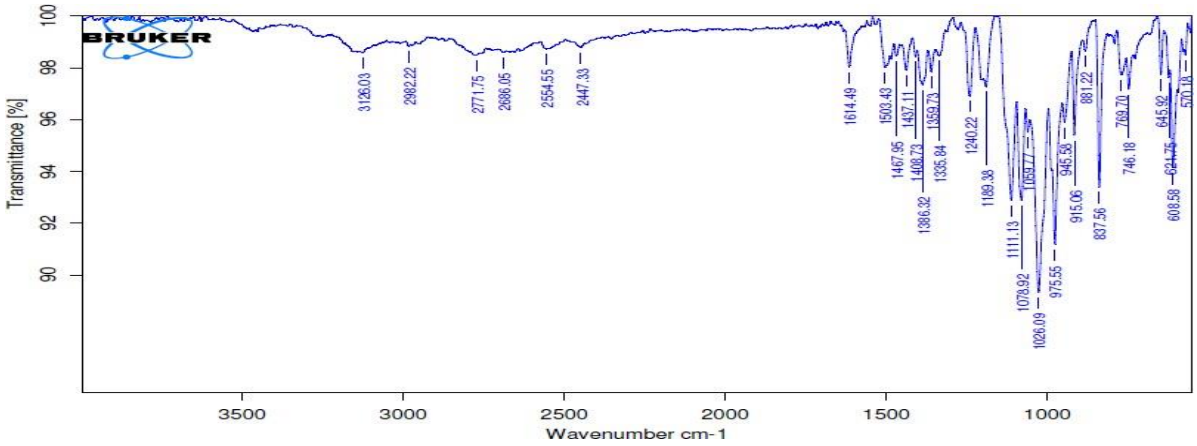

Figure5: FTIR Spectra of salbutamol sulphate

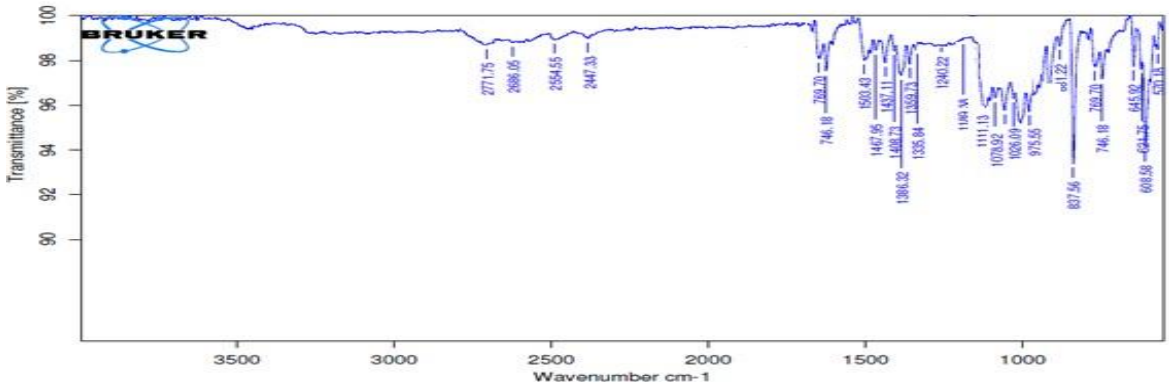

Figure 6: FTIR Spectra of pure salbutamol sulphate+excipients

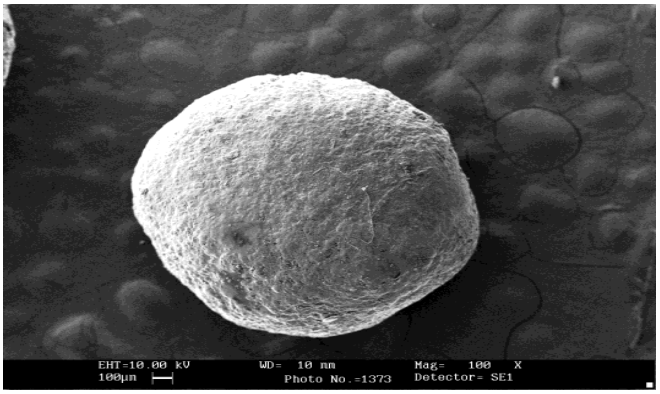

Fig7: SEM photographs of floating microspheres using sodium alginate andguar gum

Evaluation of Salbutamol Sulphate Floating Microspheres:

Surface morphology - Scanning Electron Microscopy (SEM)

Determination of Average particle size:

Table 7: Average diameter of Salbutamol sulphate floating microspheres.

Formulation code	Average size (µm)
F1	600
F2	540
F3	420
F4	320
F5	750
F6	600
F7	540
F8	520

Discussion: As the ratio of polymer was increased, the mean particle size of Salbutamol sulphate spheres had also decreased. The significant decrease may be due to the increase in the viscosity of the droplets. Salbutamol sulphate microspheres having a size range of 100 to 750 micro meter with normal frequency distribution was obtained.

Buoyancy characteristics:

Table 8: Buoyancy characteristics of Salbutamol sulphate Floating Microspheres

Sl. No.	Formulation code	Floating duration(hrs)
1	F1	7
2	F2	9
3	F3	10
4	F4	11
5	F5	12
6	F6	9
7	F7	10
8	F8	11

Table 9: Drug entrapment efficiency of Salbutamol sulphate Floating Microspheres

Sl. No.	FormulationCode	PercentageYield	Entrapment Efficiency (%)
1	F1	76.24	95.02
2	F2	78.40	96.42
3	F3	82.06	95.42
4	F4	81.08	98.71
5	F5	79.06	95.42
6	F6	53.01	97.30
7	F7	78.02	98.20
8	F8	84.15	92.44

***In vitro* dissolution studies:**

Table 10: *Invitro* evaluation of Salbutamol sulphate floating microspheres from F1-F4

Time (hrs)	F1	F2	F3	F4
0	0	0	0	0
1	41.16	36.12	29.63	29.63
2	53.36	42.86	35.64	35.64
3	61.24	50.25	42.79	42.79
4	72.16	55.67	52.15	52.15
5	80.63	62.94	60.25	60.25
6	88.75	73.42	72.63	72.63
7	95.78	80.26	86.43	86.43
8	--	90.25	96.34	91.34
9	--	97.25	--	98.34

Table 11: *Invitro* evaluation of Salbutamol sulphate floating microspheres from F5-F8

Time (hrs)	F5	F6	F7	F8
0	0	0	0	0
1	39.25	20.26	20.26	20.34
2	46.32	27.52	27.52	29.52
3	51.42	38.21	38.21	35.68
4	64.18	47.38	47.38	42.63
5	73.62	55.05	55.05	49.85
6	88.67	63.86	63.86	56.25
7	95.42	72.52	72.52	65.35
8	--	80.32	80.32	70.14
9	--	89.31	89.31	79.52
10	--	95.02	95.02	86.34
11	--	96.05	--	92.05
12	--	--	--	99.02

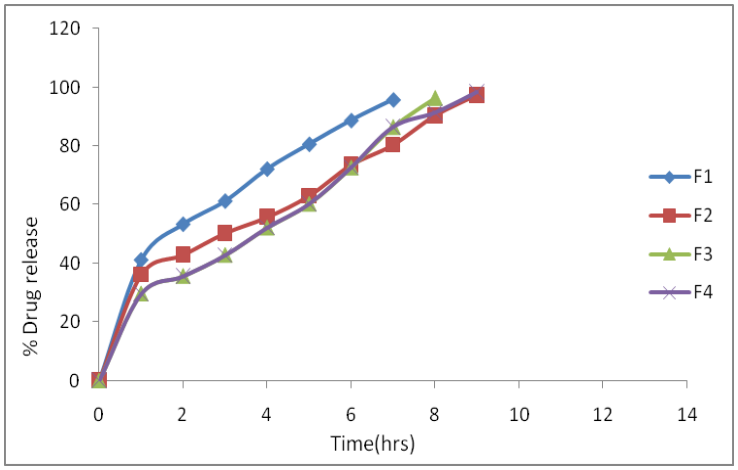

Fig 8: %Cummulative drug release of F1-F4

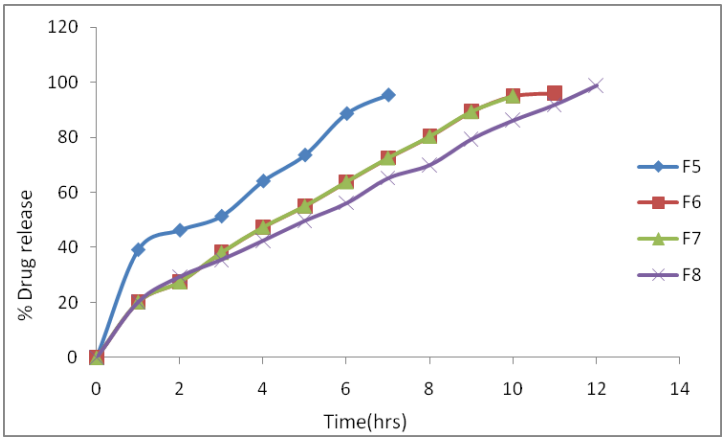

Fig9: %Cummulative drug release of F5-F8

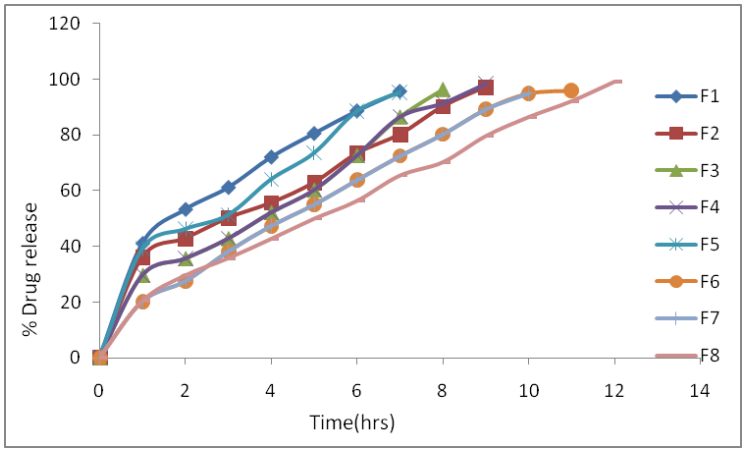

Fig10: % Cummulative drug release of F1-F8

Drug Release Kinetics: Zero Order

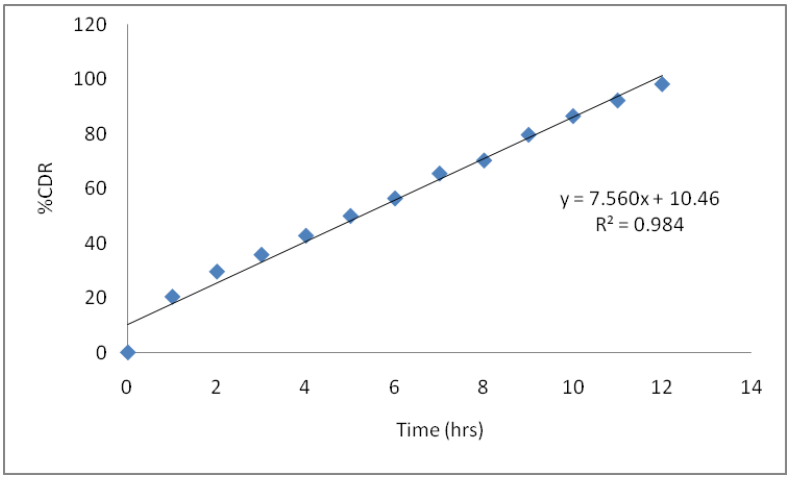

Fig11: Zero order graph of F8 formulation

First Order:

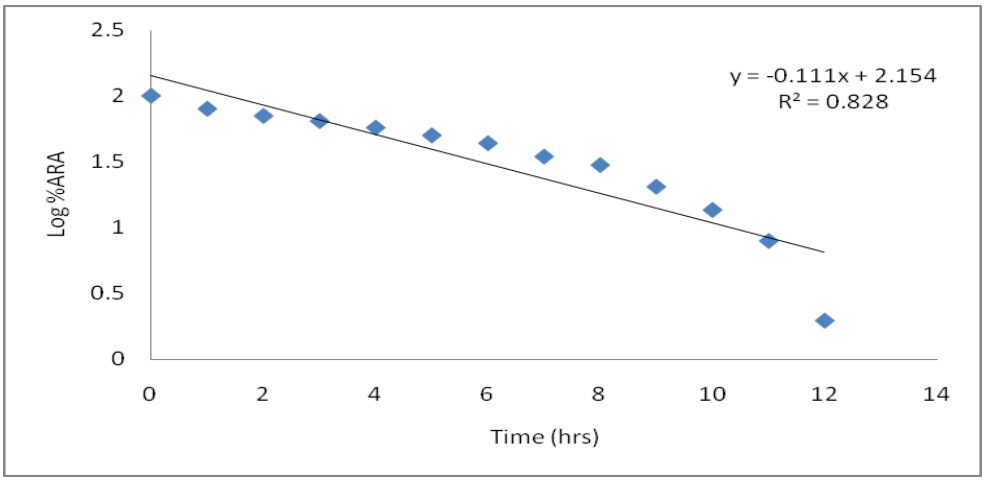

Fig 12: First order graph of F8 formulation

Higuchi plot:

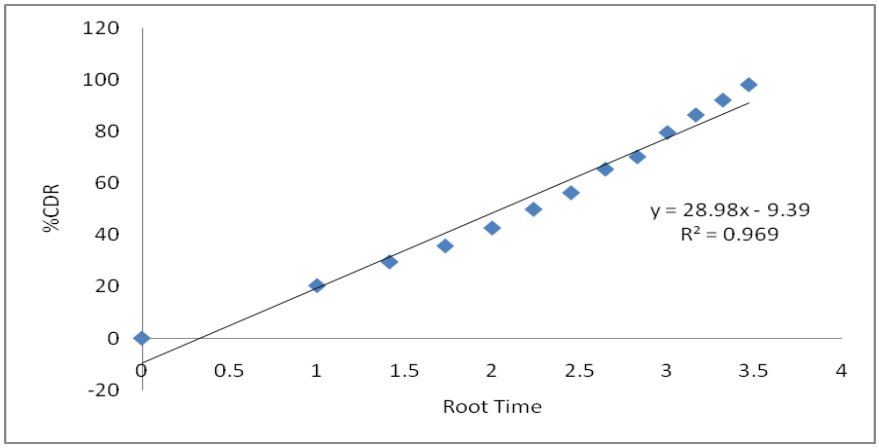

Fig13: Higuchi plot of F8 formulation

Peppas plot:

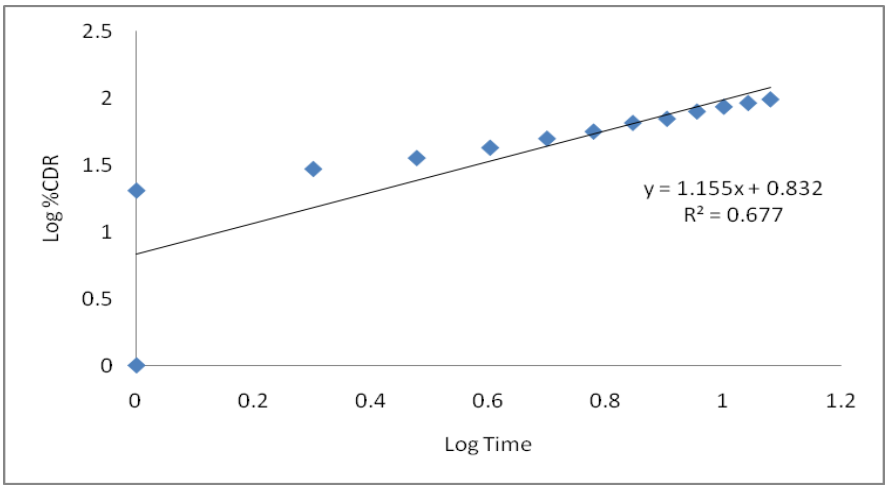

Fig14: Peppas plot of F8 formulation

Drug Release Kinetics:

Table 12: Drug Release Kinetics

Batch	ZeroOrder	FirstOrder	Higuchi	Peppas	Peppas
Code	r^2	r^2	r^2	r^2	n
F8	0.984	0.828	0.969	0.677	1.155

From the drug release kinetics of the Salbutamol sulphate floating Microspheres, it was concluded that the formulation F8 follows first order drug release with super case-II transport mechanism.

DISCUSSION:

The *invitro* dissolution data for best formulation F8 were fitted in different kinetic models i.e., zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F8 shows R^2 value 0.984. As its value nearer to the '1' it isconformed as it follows the zero-order release [14]. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot. The 'n' value is 1.155 for the optimized formulation (F8)[15] i.e., n value was >0.89 this indicates Super case II transport.

CONCLUSION:

From the above experimental results, it can be concluded that Preformulation studies like melting point, solubility and UV analysis complied with standards. The FTIR Spectra revealed that, there was no interaction between Salbutamol sulphate and polymers. Surface smoothness of the Salbutamol sulphate beads was confirmed by SEM. As the ratio of polymer was increased, the mean particle size of Salbutamol sulphate floating beads was decreased. Salbutamol sulphate floating beads with normal frequency distribution were obtained. From the results of entrapment efficiency it can be inferred that there was a proper distribution of Salbutamol sulphate in the beads and the deviation was within the acceptable limits. Polymers were taken in different concentration ratios with alone and in combination like 1:1.5, 1:2.5, 1:1:1, 1:0.5:1.5, 1:1.5:0.5, 1:1.5:1.5. The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The *in vitro* performance of Salbutamol sulphate Floating microspheres showed prolonged and controlled release of drug, with guar gum and xanthum gum with polymer concentration ratios of 1:1.5:1. Based on above results and discussion F8 formulation containing xantham gum and karayagum was proved to be best formulation as it showed maximum prolonged drug release of about 99.02% in 12 hour.

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