Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 3 Issue 4 April 2019

Research Article

Studies on Sustained Release Tablet using Ion Exchange Resins

Rahul P Gaikwad*

Principal, Uttamrao Deshmukh Institute of Pharmacy, India

***Corresponding Author:** Rahul P Gaikwad, Principal, Uttamrao Deshmukh Institute of Pharmacy, India.

Received: January 17, 2019; **Published:** March 19, 2019

Abstract

Objective: Preparation of the drug-resins complex. Performing comparatives study on different resins. Formulate the complex into sustained release tablet. Evaluate the tablet for *in-vitro* drug release. To compare *in vitro* release between marketed formulation and drug resonate formulation.

Method: Calibration curve of Salbutamol sulphate in methanol. Calibration curve of Salbutamol sulphate in simulated gastric fluid. Calibration curve of Salbutamol sulphate in intestinal fluid. Selection of resins. Preparation of drug –resins complex. Effect of various parameters on drug loading. Evaluation of resins and resinate. Physical properties. X-ray diffraction studies. I. R. Studies. Microsteriograph. *In-vitro* release of resinates. Formulation of tablet using INDION® 244. Evaluation of physical properties of tablets. *In-vitro* release profile of formulated tablets. *In-vitro* release profile of marketed tablet. f2 similarity factor between formulated preparation and marketed preparation. Stability studies of formulated tablet.

Result: The X- ray diffraction studies, I.R. studies, Microsteriograph confirms the formation of complex. The physical properties of drug, resin, and resinate, like shapes, flow properties. Bulk density, Tap density and Packing ability, were determine. Which were found to be satisfactory. *In vitro* release profile of resinate shows that more than 85% of drug release from INDION® 254, INDION® 404 in 5 and 6 hours respectively. Only 62.78% of drug was release from TULSION® 344 in 8 hours. So it is not suitable to use TULSION® 344 as sustained release. 91.14% of drug is release from INDION® 244 so resinate prepared from INDION® 244 is suitable for sustained release.

Conclusion: Conclusion was drawn that the ion exchange resins INDION® 244, coupled with tablet can serve as useful tool to sustained release of water soluble drug Salbutamol sulphate. Stability studies at 450c, RH 75%, for 1 month on tablet of batch B3 showed no significant effect on physical properties, drug content, and release profile.

Keywords: Salbutamol Sulphate; Ion Exchange Resins; Sustained Release; INDION® 254

Introduction

Ion exchange resins have received considerable attention from pharmaceutical scientist because of their versatile properties as drug delivery vehicles. In past few years ion exchange resins have been extensively studied in development of novel drug delivery system and other biomedical application [1]. Adams and Holmes were first to synthesize ion exchange resins in 1934 for their potential application in purification and separation chemicals [2]. Research over past few years discovered that ion exchange resins can be suitably adopted for drug delivery technology including controlled release, transdermal, site specific, fast dissolving, iontophoretically assisted transdermal, nasal, topical, and taste masked systems. In the recent years, considerable attention has been focused in the development of controlled release drug delivery system. The basic rationale of controlled release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of drug in such a way that its utility is maximized reduction in side effect and cure or control of condition in the short possible time by using smallest quantity of drug administered by most suitable route [3].

Sustained release dosage form

During the past few years, conventional dosage forms are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled/sustained release dosage forms

have become extremely popular in modern therapeutics. Providing sustained action after a rapid onset with decreased dosing frequency and thus enhanced patient compliance and the affording economy or reduced toxicity and minimized side effects are some of the outstanding advantages acclaimed for them [4].

Ion exchange material

Ion exchange resins are solid insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with surrounding medium, reversibly and stiochimetrically [6]. Various ion exchange materials available can be classified as shown in table 1, on basis of nature of structural and functional component and ion exchange process. The most important class, organic ion exchangers are widely used in pharmaceutical field. These include ion exchange resins, ion exchange filters and ion selective membranes (Figure 1).

Types of ion exchange resin

Ion exchange resins contain positively or negatively charged sites and are classified as either cationic or anionic exchangers. Within each category, they are classified as strong or weak, depending on their affinity for soluble counter ions. The functional group in cation exchanger and anion exchanger under goes reaction with the cations and anions of the surrounding solution respectively. The strong cation exchangers contain sulphonic acid sites INDION® 244, INDION® 254, INDION® 404, TULSION® 344 Where as weak cation exchange resin (Amberlite – IRC 50) is based on carboxylic acid moieties. The strong anion exchange resins (Dowex - 1) have quaternary amine ionic sites attached to the matrix whereas; weak anion exchangers (Amberlite IR4B) have predominantly tertiary amine substituents (Table 1).

Figure 1: Classification of Ion Exchange Resins.

Type	Exchange species	Polymers Backbone	Commercial Resins
Strong Cation Exchange Resins	$-SO_3H^+$	Polystyrene-DVB	INDION® - 244,254,404 TULSION®-344 AMBERLITE®IR120, DOWEX® 50, ZEOLIT
Weak Cation Exchange Resins	$COOH^-$	Methacrylic Acid- DVB	AMBERLITE® IRC-50
Strong Anion Exchange Resins	N^+R_3	Polystyrene-DVB	DOWEX®-1, AMBERLITE®IR400
Weak Anion Exchange Resins	N^+R_2	Polystyrene- DVB	DOWEX®2 AMBERLITE® IR4B

Table 1: Common Ion Exchange Resins.

Drug resin ratios for complex formation

The theoretical quantity of drug, which can be complexed with resins, depends upon two factors, viz.,

- The exchange capacity of resin.
- The equivalent weight of the drug.

Complex Preparation

Drug resinate (i.e. complex between resin and drug) can be prepared by two methods

1. Batch Operation.
2. Column Operation.

Important advantages [10] of ion exchange resins in formulation include

1. Economic and readily available in local market.
2. Free from local and systemic toxicities.
3. Drug-resinate (drug-resin complex) can be formulated into various dosage forms like tablets, capsules, suspension, etc.
4. Can be used for several purpose such as taste masking and retarded drug release.
5. Effectively useful in low concentration (5-20%w/w)
6. Incorporation of diluent in the formulation of low dose drugs is not essential.

7. Resins have high drug loading capacity and drug release rates are significantly retarded.

Application in drug formulation

Ion-exchange resins are used in a variety of pharmaceutical formulations like chewable or dispersible tablets, chewing gum for buccal absorption, sustained-release preparation such as capsules, liquid orals, drug stabilization, bio adhesive system and targeted delivery of anticancer drugs.

Properties of ion exchange resins [7]

Particle size

The rate of ion exchange reactions depends on the size of the resin particles. Decreasing the size of the resin particles significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium.

Porosity and swelling

Porosity is defined as the ratio of volume of the material to its mass. The limiting size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity. The porosity depends on the amount of cross-linking substance used in polymerization method. The amount of swelling is directly proportional to the number of hydrophilic functional groups attached to the polymer matrix and is inversely proportional to the degree of cross linkage.

Cross-linking

The percentage of cross-linking affects the physical structure of the resin particles, resins with low degree of cross-linking can take up large quantity of water and swell into a structure that is soft and gelatinous. However, resins with high DVB content swell very little and are hard and brittle.

Available capacity

The capacity of an ion exchanger is quantitative measure of its ability to take up exchangeable counter ions.

Acid-base strength

It depends on the various inorganic groups, incorporated into the resin. Resin containing sulphonic phosphoric or carboxylic acid exchange groups have approximate pKa values of <1, 2-3 and 4-6 respectively. Anionic exchangers are quaternary, tertiary or Secondary ammonium group having pka values >13,7-9 or 5-9 respectively. The pka values of the resins will have significant influence on the rate at which the drug will be released in the gastric fluid.

Stability

The Ion exchange resins are inert substances at ordinary temperature and excluding the more potent oxidizing agent is resistant to decomposition through chemical attack. These materials are indestructible. They get degrades and degenerated in presence of strong gamma rays.

Purity and toxicity

Since the resins combination contains 60% or more of the resins, it is necessary to establish its toxicity. Commercial products cannot be used, as such careful purification of resins is requiring. Resins are not absorbed by body tissue and are totally safe for human consumption. Test for toxicological tolerance showed that it does not have any pronounced physiological action at recommended dosage and it definitely non - toxic.

Mechanism and principle [7,14]

Anion exchange resins involved functional group (usually a poly amine) capable of removing anions in acidic solution. Cation exchange resins contain acidic functional groups. Although their exact composition may vary, they usually contain polystyrene polymers with sulphonic or carboxylic or phenolic group. The use of ion exchange resins to prolong the effect of drug is based on the principle that positively or negatively charged drug moiety combined with appropriate resins yield insoluble polysalt resinate.

$$R\text{-}SO^{-}_{3}\text{-}H^{+} + H_2N\text{-}A \leftrightarrow R\text{-}SO^{-}_{3} - H_3N\text{-}A$$

$$R\text{-}N^{+}H_3OH + HOOC\text{-}B \leftrightarrow R\text{-}N^{+}H_3\text{-}OOC\text{-}B + H_2O$$

Where H2N-A and HOOC-B represent a basic and acidic drug respectively and R-SO3-H+ and R-NH3-OH- represent cationic and anionic ion exchange resins respectively. The slow release of drug from ion exchange resins was recognized by saunder and srivastava[15] (1980), as a suitable approach to design of sustained release preparation. Resinate administered orally are likely to spend about 1-2 hours in the stomach in contact with an acidic fluid of pH 1.2 and then moves into intestine where they will be in contact for more than six hours with a fluid of slightly alkaline pH[7].

In the stomach,

R-SO-3 - H3 N+-A + HCL ↔ R-SO3-H+ + A-N+H3CL

R-N+H3-OOC-B + HCL ↔ R-N+H3CL+ + B-COOH

In the intestine

R-SO-3 - H3 N-A +NACL ↔ R-SO3-NA+ +A-N+H3 CL-

R-N+H3- OOC-B +NACL ↔ R-N+H3CL- + B-COO-NA+

Applications

1. Sustained Release
2. Taste Masking
3. Tablet Disintegrant
4. Drug Stabilization
5. Cholesterol Reducer
6. Recent Advances

In last few years, the fairly new applications for ion exchange resins have been noticed. Avari and Bhalekar reported improved dissolution of sparfloxacin bound to weak cation exchanger. They reported faster dissolution of this poorly soluble drug bound to weak cation exchanger INDION® 204, as compared to marketed formulation11. Recent use of ion exchange resins for potential nasal delivery of insulin have been reported37. Ion exchanger for ocular delivery of betoxolol increased ocular comfort and increased bioavailability [38]. Ion exchange resins have also been used for site specific [39,40] and transdermal drug delivery [41-43].

Factors affecting formulation and drug release from complex [7]

1. Cross linking of resin
2. Particle size
3. Ph
4. Form of resin
5. Size of exchanging ion
6. Selectivity of counter-ion
7. Mixing time
8. Effect of temperature

Rationale of sustained drug release [44]

The basic rational for sustained drug delivery is to alter the pharmacokinetic and pharmacodynamic's of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and or physiological parameters inherent in a selected route of drug administration. It is desirable that the duration of drug action become more design property of a rate controlled dosage form and less or not at all a properties of a drug molecule's inherent kinetic properties. Thus optimal design of controlled release systems necessitates a thorough understanding of the pharmacokinetic and pharmacodynamic of the drug.

Materials and Methods

Literature Survey: Literature survey reveals following studies were previously performed to develop the sustained release formulation of basic drug using strong cation exchange resins.

1. S.P. Manek and V.S. Kamat have reported [10] "The Preparation and Evaluation of INDION CRP 244 and CRP 254 as a sustained release agent".

2. Gernald M, Burke, Robert W Mendes and Sunil. S. Jambekar reported the applicability of strong cation exchange resins as a sustained release tablet of Propranolol HCL [2].

3. Saul Borodkin, Martin H. Yunker reported the interaction of amines drug with a polycarboxylic acid ion exchange resins [14].

4. Chaudhry., *et al*. (1956) studied the uptake and release of ephedrine, dexamphetamine from carboxylic acid type resin and sulphonic acid resin, found that, sulphonic acid resin gives a more moderate release than carboxylic acid resin [15].

Materials

Salbutamol sulphate [41,42]

Figure 2

Molecular Weight: 576.70
Melting Point: 1560C
pKa: 9.3,10.3
CAS Registry Number {51022-70-9}

Solubility

Freely soluble in water; slightly soluble in ethanol (95%) and in ether; very slightly soluble in dichloromethane.

Physical properties

White or almost white, crystalline powder odourless or almost odourless with bitter taste.

Pharmacology

Salbutamol is a selective β2 adrenoreceptor agonist, with effects on smooth and skeletal muscle. These induce bronchodilation, relaxation of uterine muscle and tremor. Smooth muscle relaxation thought to occur via adenyl cyclase-cyclic adenosine monophosphate (cAMP) system, with binding of drug to β-adrenergic receptor in the cell membrane causing conversion of ATP to cAMP, which activates protein kinase. This leads to phosphorylation of protein which increases bound intracellular calcium, the consequent reduced availability of ionized calcium inhibits actin-myosin linkage thus causing relaxation of smooth muscles.

Pharmacokinetics

Salbutamol is well absorbed from gastrointestinal tract (85%) and has considerable presystemic metabolism. The plasma half life varies between 2.7 to 5 hours (mean 3.8 hrs). The mean volume of distribution after intravenous infusion is 3.4 ± 0.61 kg. The plasma protein binding was reported to be 10%.

Therapeutic uses

1. Bronchodilator for use in asthma, chronic bronchitis, and other conditions associated with airways obstruction.
2. In management of premature labour.

Dosage recommendation

Orally the equivalent of 6 to 16 mg of Salbutamol three or four times daily in divided doses. By slow intravenous injection, the equivalent of 250 µg of Salbutamol or by intravenous infusion, the equivalent of 3 to 20 µg of Salbutamol per minute.

Preparation Available

- Tablet: 2 mg, 4 mg and 8 mg.
- Sustained Release Tablet: Usual strength 4 mg and 8 mg
- Syrup: The equivalent of 2 mg of Salbutamol in 5 ml.

Carrier profile

INDION® 244 [40]

INDION®244 is a high purity pharmaceutical grade strong acid cation exchange resin, supplied in hydrogen form as a free flowing powder. It is suitable for sustained release and taste masking of bitter drugs. It is based on a styrene and divinyl benzene co-polymer.

Characteristics

Physical

- Appearance: Light brown coloured powder, free from foreign matter.
- Matrix: Cross-linked polystyrene.
- Solubility: Insoluble in water and all common solvents.
- Ionic form: Hydrogen.
- Moisture content: 10% maximum.

Particle size

Retained on 100, BSS mesh (150 microns) - 1% maximum, Retained on 200, BSS mesh - 45% maximum.

Chemical

- Functional group - SO3H
- Ion exchange capacity - 4.5meq/dry gm, min.

Application

Sustained release agent

INDION® 244 finds application as a sustained release agent to have prolonged and predictable drug release characteristic. INDION®244 imparts sustained release properties to oral dosage forms through the formation of drug- resins complex. The drug is released from the resinate *in-vivo* as it reaches equilibrium with the high electrolyte concentration which is typical of gastro-intestinal tract.

Taste masking

When used as a drug carrier, INDION® 244 provides a mean for binding the active drug. This can afford an effective means for minimizing the problem of taste and odour, which may associate with the drug.

Toxicity

INDION® 244 is a high molecular weight crosslinked polymer. It is therefore not absorbed by body tissues and is totally safe for human consumption. Tests for toxicological tolerance show that it does not have any pronounced physiological action at recommended dosage levels and is definitely non-toxic. Experiments on Mice have shown LD50 value of INDION® 244 to be approximately 5,500mg/kg body weight.

Packaging Standard packaging of INDION® 244 is in HDPE container with inner plastic bags 6kg jars or 40kg drums.

INDION® 254 [50]

INDION® 254 is a high purity pharmaceutical grade strong acid cation exchange resin, supplied in sodium form as a free flowing powder. It is suitable for sustained release and taste masking of bitter drugs. INDION® 254 is derived from a sulphonated co-polymer of styrene and divinyl benzene co-polymer. INDION® 254 confirms to specification of monograph for sodium polystyrene sulphonate in USP/NF.

INDION® 404 [50]

INDION® 404 is a high purity pharmaceutical grade strong acid cation exchange resin, supplied in calcium form as a free flowing powder. It is suitable for sustained release and taste masking of bitter drugs. INDION® 404 is derived from a sulphonated co-polymer of calcium polystyrene. INDION® 404 confirms to specification of monograph for calcium polystyrene sulphonate given in B.P.

List of chemicals

- Salbutamol Sulphate - Medicore Laboratories, Paithan.
- INDION® 244 - Ion Exchange India Ltd, Mumbai.
- INDION® 254 - Ion Exchange India Ltd, Mumbai.
- INDION® 404 - Ion Exchange India Ltd, Mumbai.
- TULSION® 344 -Thermax Ltd, Pune.
- Microcrystalline Cellulose (Avicel PH 102) - Signet Chemical Corporation, Mumbai.
- Magnesium Stearate - Loba Chem, Mumbai.
- Talc - Venus Chemical's

List of equipment's

- Single pan balance - Citizen CTG 302.
- pH Meter - Hanna Instruments.
- Magnetic stirrer - Labtech.
- U.V. Spectrophotometer - Milton Roy (SPECTRONIC 21D).
- Dissolution Apparatus - Veego.
- Tablet Machine - Cadmach Machinery Co. Pvt. Ltd.
- Friabilator - Roche Friabilator.
- Hardness tester - Dolphin Mumbai.

Methods

Experimental work

INDION®244 is a high purity pharmaceutical grade strong acid cation exchange resin, supplied in hydrogen form as a free flowing powder. It is suitable for sustained release and taste masking of bitter drugs. It is based on a styrene and divinyl benzene co-polymer.

1. Selection of Resin
2. Moisture content determination of resins [53]
    - Calibration curve of salbutamol sulphate
    - Calibration curve of salbutamol sulphate in methanol
    - Calibration curve of salbutamol sulphate in gastric simulated fluid without enzyme
    - Calibration curve of salbutamol sulphate in intestinal fluid without enzyme
3. Resin pretreatment
4. Preparation of the drug resin complexes (resinates)
    - The resinate were prepared by batch process. An accurately weighed amount of Salbutamol sulphate (1 g in all instances) was taken and dissolved in 100 ml of distilled water. Then a known weight of ion exchange resin was added to the solution and was stirred on a magnetic stirrer. Time to reach equilibrium was determined by periodically measuring concentration of the drug in solution spectrophotometrically. It was found that 4 hours is the optimum period for the attainment of the loading equilibrium. Resinate thus formed was filtered and washed with deionized water. It was then dried at 50^0 C and the drug content was determined spectrophotometrically at 276 nm.
5. Determination of drug content in the resinate
6. Effect of ph on drug loading
7. Selection of drug resin ratio
8. Effect of mixing time on drug loading
9. Effect of temperature on drug loading
10. Physical properties of resins and resinate
11. X –ray diffraction studies
12. I.R. Studies
13. Microsteriograph
14. *In vitro* release profile of resinate

Results and Discussion

Calibration curve of salbutamol sulphate in methanol

The calibration curve of Salbutamol sulphate in methanol in the concentration range of 2-20µg/ml was found to pass through the origin and was a straight line. Thus it followed the Beer Lambert law (Figure 3).

Figure 3

Calibration curve of salbutamol sulphate in gastric simulated fluid without enzyme (pH 1.2)

Various drug concentrations (5-50µg/ml) in gastric fluid (without enzyme) were prepared and the absorbance was measured at 276nm. For the standard graph, 60.0mg of Salbutamol sulphate equivalent to 50 mg of Salbutamol was accurately weighed and dissolved in 50ml of gastric fluid, 25 ml of the solution was diluted 250ml with gastric fluid. Then 2.5ml, 5ml, 7.5ml, 10ml, 12.5ml, 15ml, 17.5ml, 20ml, 22.5ml, 25ml of this solution was further diluted to 50ml with gastric fluid and the absorbance was taken at 276nm using spectrophotometer (Figure 4).

Figure 4

Calibration curve of salbutamol sulphate in intestinal fluid without enzyme

Various drug concentrations (5-50µg/ml) in intestinal fluid (without enzyme) were prepared and the absorbance was measured at 276nm. For the standard graph, 60.0mg of Salbutamol sulphate equivalent to 50 mg of Salbutamol was accurately weighed and dissolved in 50ml of intestinal fluid 25 ml of the solution was diluted 250ml with intestinal fluid. Then 2.5ml, 5ml, 7.5ml, 10ml, 12.5ml, 15ml, 17.5ml, 20ml, 22.5ml, 25ml of this solution was further diluted to 50ml with intestinal fluid and the absorbance was taken at 276nm using spectrophotometer (Figure 5).

Figure 5

Effect of pH on drug loading

The loading of Salbutamol sulphate onto ion exchange resin is equilibrium process, which depends upon the presence of cationic form of the drug in the solutions. The presence of cationic form of drug is influenced by pH of the solution, which therefore exerts an influence on loading efficiency. To investigate this behavior, the pH of the Drug Resin solution was varied keeping the drug resin in the ratio 1:1. The result showed that at pH 5.5 maximum loading of drug on the resin occurs. Shown in figure.

Effect of Ph on drug loading

PH	% Drug content per gram of resinate			
	INDION® 244	INDION® 254	INDION® 404	TULSION® 344
3	54.23	45.23	43.65	49.50
3.5	54.04	45.21	43.32	49.15
4	55.99	45.96	45.99	50.12
4.5	56.48	47.33	46.55	51.99
5	57.75	47.99	46.93	52.53
5.5	59.24	49.85	48.16	53.65
6	52.69	47.12	44.27	49.99

Table 2

Figure 6

Selection of drug resin ratio

For the selection of the proper drug resin ratio, the ratio of the drug resin was varied, keeping concentration of drug constant. The pH of the solution was maintained at 5.5. The results shows that drug resin in the ratio of 1:1 has better drug loading as compared to the other.

Drug: resin Ratio	% Drug loading			
	INDION® 244	INDION® 254	INDION® 404	TULSION® 344
1:1	59.30	49.99	48.73	53.84
1:1:5	55.64	44.46	46.10	51.58
1:2	52.35	41.17	42.41	50.48
1:3	49.25	39.51	40.13	48.64

Table 3

Figure 7

Effect of mixing time on drug loading

The effect of mixing time was examined by measuring the drug loading of resin that had been mixed with the acidified drug solution for different length of time. The result shows that maximum binding occurs in approximately 4 hours.

Effect of time on drug loading

Time in Minutes	% Drug Loading			
	INDION® 244	INDION® 254	INDION® 404	TULSION® 344
30	44.25	32.48	30.82	37.58
60	48.66	35.33	35.00	39.20
90	51.15	40.66	36.53	40.89
120	52.89	43.07	38.89	44.94
150	54.69	44.71	40.15	47.05
180	55.05	46.38	42.28	49.05
210	56.92	47.30	45.28	51.07
240	59.30	49.99	48.73	53.84
270	59.30	49.98	48.74	53.85

Table 4

Figure 8

Temp	% Drug content per gram of resinate			
	INDION® 244	INDION® 254	INDION® 404	TULSION® 344
30°C	55.36	44.52	45.73	51.02
35°C	59.30	49.99	48.73	53.84
40°C	58.05	46.65	46.12	51.65
45°C	56.47	45.22	47.20	49.44
50°C	53.14	40.99	43.85	50.58
55°C	54.88	41.12	40.83	45.48
60 ° C	50.75	40.90	41.84	44.99

Table 5

Effect of temperature on drug loading

A series of solution were prepared containing 1g of Salbutamol sulphate and 1g of resins i.e. INDION® 244, INDION® 254, INDION® 404, and TULSION® 344.The pH of all these solution was maintained at 5.5 pH. These were stirred on magnetic stirrer at room temperature 30°C, 35°C, 40°C, 45°C, 50°C, 55°C and 60° C (Table 5 and Figure 9).

Effect of temperature on drug loading

(Table 6)

Figure 9

Character	Indion® 244 resins	Resinate	Indion® 254 resins	Resinate	Indion® 404 resins	Resinate	Tulsion® 344 resins	Resinate
Shape	Spherical	Irregular	Irregular	Irregular	Irregular	Irregular	Irregular	Irregular
Angle of Repose	30.42	31.14	28.56	29.12	29.78	30.76	29.34	29.76
Bulk Density	0.666	0.670	0.667	0.685	0.640	0.612	0.607	0.620
Tap Density	0.755	0.766	0.758	0.785	0.712	0.693	0.680	0.695
Carr, s Index	11.78	12.53	12.00	12.73	10.11	11.68	10.73	10.79
Hausner Ratio	1.13	1.14	1.13	1.14	1.11	1.13	1.12	1.12

Table 6

X –Ray diffraction studies

Figure 10: XRD report of salbutamol sulphate.

Figure 11: XRD report of physical mixture of drug and resins.

Figure 12: XRD report of resins 244.

Figure 13: XRD report of resinate of drug and resins 244.

IR studies

The Salbutamol sulphate, resins, resinate and blend of tablet were subjected to I.R. studies for incompatibility determination. It was found that there is no incompatibility occurs in the I.R. Report.

Figure 14: I.R. report of salbutamol sulphate.

Figure 15: I.R. Report INDION 244 Resin.

Figure 16: I.R. Report of INDION 244+Salbutamol.

Figure 17: I.R. Report of Tablet Blend.

Microsterio graph

By using the Microsteriograph the resin and the resinate were observed. The results are given below which indicates the binding of drug onto the resin.

Figure 18: Microsteriograph of Resin Indion 244.

Figure 19: Microsteriograph of Resinate.

In-Vitro Release Profile of Resinate

The release of Salbutamol sulphate was studied using Usp 24, type II dissolution apparatus at 50 rpm for 2 hours in 1.2 pH buffer and for further 6 hours in 6.8 pH phosphate buffer.

Figure 20: *Invitro* Drug Release Profile of Resinate.

Formulation of Tablets

Resinate of Salbutamol sulphate and INDION® 244 was formulated into a tablet. Following ingredients are also used Microcrystalline cellulose is used as filler, binder. Talc is use as glidant and Magnesium sterate is used as lubricant. Both these excipients are used in tablet. Various batches (B1-B5) of tablet were formulated with resinate and different concentration of excipient as shown in table

Formula for the preparation of tablets

Ingredient %W/W	Batches				
	B1	B2	B3	B4	B5
INDION® 244 Resinate	21.6	21.6	21.6	21.6	21.6
Avicel 102	75.9	75.9	76.9	76.4	76.4
Talc	0.5	1.5	0.5	1	0.5
Magnesium Sterate	2	1	1	1	1.5

Table 7

Evaluation of physical properties of tablets

Test Parameter	Batch				
	Batch B1	Batch B2	Batch B3	Batch B4	Batch B5
Hardness (Kg/cm^2)	4.30	5.20	5.10	4.70	5.25
% Friability	0.442	0.376	0.389	0.417	0.367
Thickness	2.0	2.3	2.1	2.3	2.4
Wt variation ± 10.00	Passes	Passes	Passes	Passes	Passes
Content uniformity (%)	97.50	97.35	98.37	97.82	96.99
Disintegration Time (Sec)	20	15	14	16	19

Table 8

Evaluation of *In-Vitro* release profile of formulated tablets

In-vitro release profile of tablets

Time in hours	Dissolution Medium	Cumulative % drug release				
		B1	B2	B3	B4	B5
1	1.2 pH Buffer	17.38	15.07	13.91	20.86	23.18
2	1.2 pH Buffer	24.34	23.18	23.18	27.81	32.45
3	6.8 pH Buffer	37.93	40.17	39.04	48.20	56.24
4	6.8 pH Buffer	48.13	45.83	50.36	59.53	68.70
5	6.8 pH Buffer	60.59	59.43	62.83	67.46	78.89
6	6.8 pH Buffer	74.18	70.76	74.15	77.66	87.96
7	6.8 pH Buffer	87.77	79.82	86.62	86.72	92.48
8	6.8 pH Buffer	94.57	91.14	90.01	92.38	94.75

Table 9

Figure 21

Comparison of drug release with USP Criteria

TIME (Hr)	Cumulative % of drug release	
	USP	B3
1	10-21	13.91
2	18-33	23.18
3	31-50	39.04
5	50-82	62.83
8	N. L. T. 85	90.01

Table 10

Comparison of in-vitro release profile of formulated salbutamol tablet (b3) with marketed tablet

The comparative in-vitro drug release profile of marketed tablet (Asthalin-SA) and formulated batch (B3) serves as guide estimating the amount of drug release per unit time. It is also indirectly used to assess the physiological and biological activity of drug molecule (Figure 22).

f2 Value

Table 11

Figure 22

Batch Codes:	Test	B3
	Ref	MKTD
f2 (Similarity Factor)		99.70

Table 11

Stability studies of tablets

Effect of temperature on physical properties and drug content

Batch	Hardness	% Friability	Thickness	Drug content (mg)	Disintegration Time (Sec)
B3	5.18	0.380	2.1	7.87	14

Table 12

Effect on *in vitro* drug release

Batch	Time (Hours)	Cumulative % Drug Release
B3	1	13.75
	2	22.85
	3	38.31
	4	40.36
	5	61.99
	6	73.27
	7	85.77
	8	89.12

Table 13

Conclusion

Salbutamol sulphate is one of such drug widely used in asthma with increased mucous secretion and in chronic bronchitis. Salbutamol sulphate is a potent β_2 adrenoreceptor agonist. It is freely soluble in water. It has quick onset of action and short half-life i.e. 2.7-5 hours (mean 3.8 hours). The dose of conventional tablet is T.I.D. It is tedious for the patient. Optimization of drug action including drug safety and patient compliance may often be achieved by controlling the rate of drug delivery from the dosage form. The sustained release of Salbutamol sulphate (modeled drug) were formulated by using ion exchange resins. In the present work ion exchange resins like INDION® 244, INDION® 254, INDION® 404 and TULSION® 344 were selected. Ion exchange resins were chosen for sustained the drug release because the resinate formulation offers additional advantage over other sustained release formulation are

1. Factors influencing rate of release of drug from ion exchange matrices, such as competing ions, ionic strength and pH relatively fixed by condition within the gastro intestinal Tract.
2. Resins characteristics such as acid base strength, porosity, degree of cross linking and particle size can be chosen from among many available ion exchange resins to achieved intended purpose.
3. Better drug retaining properties and prevention of dose dumping.
4. The polymeric (physical) and ionic (chemical) properties of ion exchange resins will release the drug more uniformly than that of simple matrices.
5. Complete sustained release.
6. Economical.
7. Minimum preparation time.

Conclusion was drawn that the ion exchange resins INDION® 244, coupled with tablet can serve as useful tool to sustained release of water soluble drug Salbutamol sulphate. Stability studies at 450c, RH 75%, for 1 month on tablet of batch B3 showed no significant effect on physical properties, drug content, and release profile. Thus INDION® 244 Salbutamol sulphate when formulated as tablet using Avicel, Magnesium Sterate and Talc provided sustained release, which satisfied the criteria for sustained release, Zero order release and good stability is observed. Thus, formulated tablet provide pH independent sustained release of Salbutamol sulphate and good stability.

Future Scope

To formulate various formulation using different Resins and compare with the present formulation. To formulate the formulation containing combination of drugs. To study Drug and Resin interaction by D.S.C.

Bibliography

1. V anand., *et al*. "Ion-exchange resins; carrying drug delivery forward". *Drug Discovery Today* 6 (2001): 905-913.

2. GM Burke., *et al*. "Investigation of the applicability of ion exchange resins as a sustained release drug delivery system for propranolol Hydrochloride". *Drug Development and Industrial Pharmacy* 12 (1986): 713-732.

3. YW Chein. "Potential Development and New Approaches Controlled Release Drug Delivery Systems". Marcel Dekker, Inc. New York (1983): 1251-1380.

4. "International Symposium of Controlled Release Dosage Form". BCP-IPA (1987).

5. NK Jain. "Controlled and Novel Drug Delivery". 1st Edition 1-49 (1997):

6. Y Raghunathan., *et al*. "Suatained-release drug delivery system I coated ion exchange resin system for phenylpropranolamine and other drugs". *Journal of Pharmaceutical Sciences* 70 (1981): 379-384.

7. M Vimaladevi., *et al*. "Advances in Controlled and Novel Drug Delivery". 1st Edition (Edition NK Jain): CBS publishers and Distributors, New Delhi (2001): 290-305.

8. AV Kulkarni. "Indian speciality resins as pharmaceutical excipient, Literature provided by Ion Exchange India Ltd. (Mumbai).

9. DM Brahmankar., *et al*. "Biopharmaceutics and Pharmacokinetics, A Treaties". 1st Edition Vallabh Prakashan, New Delhi, (1995): 335-357.

10. SP Manek., *et al*. "Evaluation of INDION CRP-244 and INDION CRP-254 as sustained release and taste masking agents" *Indian Journal of Pharmaceutical Sciences* 43 (1981): 209-212.

11. JG Avari and Bhalekar. "Cation exchange resin for taste masking and rapid dissolution of sparfloxacin". *Indian Drugs* 41 (2004): 19-23.

12. DA. Schilichting. "Ion exchange resin salts for oral therapy I carbinoxamine". *Journal of Pharmaceutical Sciences* 51 (1962): 134-136.

13. M Sriwongjanya., *et al*. "Effect of ion exchange resin on the drug release from matrix tablets". *European Journal of Pharmaceutics and Biopharmaceutics* 46 (1998): 321-327.

14. S Borodkin. "Ion exchange resins and sustained release". In: J. Swarbric, J. Boylan (Editions.): Encyclopedia of Pharmaceutical Technology, Marcel Dekker, New York, 8 (1996): 203-216.

15. NC Chaudhary and S Luanders. "Sustained release of drugs from ion exchange resins". *Journal of Pharmacology* 8 (1956): 975-985.

16. NG Lordi. "Sustained release dosage forms". In: L. Lachman, H.A.Liberman, J.L. Kanig (Editions.): The Theory and Pratice of Industrial pharmacy, Varghese Publishing House, Mumbai (1991): 450-451.

17. S Mytycka and JG Nairn. "Influence of wax coatings on release rate of anions from ion exchange resin beads". 67 (1978): 500-503.

18. S Mytycka and JG Nairn. "Influence of wax coatings on release rate of anions from ion exchange resin beads". *Journal of Pharmaceutical Sciences* 74 (1985): 643-646.

19. WJ Irwin., *et al*. "Alpar Drug- delivery by ion exchange part III: interaction of ester prodrug of propranolol with cation exchange resins". *Drug Development and Industrial Pharmacy* 13 (1987): 2047-2065.

20. NM Sanghavi., *et al*. "Ion exchange resins as matrices for controlled drug release". *Indian Drugs* 26 (1988): 217-222.

21. OL Sprokcel., *et al*. "Effect of eluent properties on drug release from cellulose acetate butyrate coated drug resin complexes". *International Journal of Pharmaceutics* 48 (1988): 217-222.

22. JR Woodworth., *et al*. "Comparative Bioavailability of a sustained release Ion-exchange hydralazine product with a potassium (cation): challenge". *Journal of Pharmaceutical Sciences* 81 (1992): 541-542.

23. JA Plaizier-Vercammen. "Investigation of the bioavailability of codeine from cation exchange sulphonic acid 1 effect of parameters". *International Journal of Pharmaceutics* 85 (1992): 45-50.

24. JA Plaizier-Vercammen. "Investigation of the bioavailability of codeine from cation exchange sulphonic acid 2 effect of parameters". *International Journal of Pharmaceutics* 87 (1992): 31-36.

25. P Akkaramongkolporn., *et al*. "Molecular state of chlorpheniramine in resinate". *Chemical and Pharmaceutical Bulletin* 48 (2000): 431-434.

26. M Cuna., *et al*. "Controlled release liquid suspension based on ion exchange particles entrapped within acrylic microcapsules". *International Journal of Pharmaceutics* 199 (2000): 151-158.

27. P Akkaramongkolporn., *et al*. "Molecular properties of propranolol hydrochloride in resinate". *Drug Development and Industrial Pharmacy* 27 (2001): 359-364.

28. H Sohi., *et al*. "Taste masking technologies in oral pharmaceutical's: Recent develoment and approaches". *Drug Development and Industrial Pharmacy* 30 (2004): 429-448.

29. H Sugao., *et al*. "Taste masking of bitter drug powder without loss of bioavailability by heat treatment of wax coated microparticles". *Journal of Pharmaceutical Sciences* 87 (1998): 96-100.

30. P Borodkin., *et al*. "Polycarboxylic acid ion exchange resin adsorbates for taste coverage in chewable tablets". *Journal of Pharmaceutical Sciences* 60 (1971): 1523-1527.

31. R Agrawal., *et al*. "Studies of Ion-exchange resin complex of chloroquine phosphate". *Drug Development and Industrial Pharmacy* 26 (2000): 773-775.

32. www.rohmhass.com/ionexchnge/phrmaceuticals/polymerph.htm

33. www.rohmhass.com/ionexchnge/phrmaceuticals/stabilisation.htm

34. M takenaga., *et al*. "Microparticle resin as a potential nasal drug delivery system for insulin". *Journal of Controlled Release* 52 (1998): 81-87.

35. R Jani., *et al*. "Ion exchange resins for ophthalmic delivery". *Journal of Ocular Pharmacology* 1 (1994): 57-67.

36. Y Chen., *et al*. "Evaluation of ion exchange Microspheres as carrier for the anticancer drug doxorubicin in-vitro studies". *Journal of Pharmaceutical Sciences* 44 (1992): 211-215.

37. S Burton., *et al*. "Intragastric distribution of ion exchange resin as a drug delivery system for the tropical treatment of gastric mucosa". *Journal of Pharmaceutical Sciences* 47 (1995): 901-906.

38. T Jaraski., *et al*. "Controlled transdermal iontophoresis by ion exchange fiber". *Journal of Controlled Release* 70 (2001): 219-229.

39. J Hirvonen., *et al*. "Effect on diffusion potential osmosis and ion exchange on transdermal drug delivery: theory and experiments". *Journal of Controlled Release* 56 (1998): 33-39.

40. SB Kuchekar., *et al*. "Mouth dissolving tablets of salbutamol sulphate: A. novel drug delivery system". *Indian Drugs* 41 (2004): 592-598.

41. Indian Pharmacopoeia, Vol II, Published by controller publication, Delhi (1996): 670-671.

42. Therapeutics Drugs, (Sir Collin Dollery Edition): Churchill Vingstone2 (1991): 51-54.

43. Indian Pharmacopoeia, Vol II, Published by controller publication, Delhi (1996): 111-112.

44. LSC Wan. "Manufacture of Core pellets by Balling, in Multiparticulate Oral Drug Deliver". Edition Issac, Ghebre, Sellassie, Marcel Dekker, New York (1994): 1-16.

45. Mehta RM. "Pharmaceutics I". Third Edition; 7 (2002): 238.

46. Lachman L and Liberman HA. "Theory and Practice of Industrial Pharmacy". Third Edition (1990): 293-294.

47. Lachman L and Liberman HA. "Theory and Practice of Industrial Pharmacy"; Third Edition (1990): 329-335.

48. Liberman HA. "Pharmaceutical Dosage Forms; Tablets". Second Edition 1 136

49. Liberman HA. "Pharmaceutical Dosage Forms; Tablets". Second Edition 1 198-199.

50. Literature provided by Ion Exchange India Limited Mumbai.

51. Literature provided by Thermax India Limited Pune.

52. H Kibbe. "Handbook of Pharmaceutical Excipients". 3rd Edition The American Pharmaceutical Association, Washington, DC (1986): 102-106.

53. AS Rankell., *et al*. "The Theory and Practice of Industrial Pharmacy". Varghese Publishing House, Bombay, (1991): 47-53.

54. Remington "The Science and Practice of Pharmacy". 19th Edition 1 (1605): 1669-1670.

55. GS Banker., *et al*. "The Theory and Practice New uses of Ion exchange resin in pharmaceutical formulation". Dr. L.Hughes Rohm And Hass Research Laboratories.

56. J Keating. U.S. Patent No. 2,990,332 (1961).

57. Raymond CR., *et al*. "Handbook of Pharmaceutical Excipient". 4th Edition 108-111.

58. S Siegel., *et al*. "Tablets of pyrilamine resin adsorbate with aspirin and vitamin C". *Journal of Pharmaceutical Sciences* 51 (1962): 1068-1071.

59. SN Meheshendale., *et al*. "Ion-exchanger in the pharmaceutical industry, Eastern Pharmacist Martindale". The Complete Drug Reference. 33rd Edition (1991): 770-773.

Volume 3 Issue 4 April 2019