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NOVEL SUPERDISINTEGRANTS INTERPOLYMERIC CHITOSAN-ALGINATE COMPLEX AND CHITIN IN THE FORMULATION OF ORODISPERSIBLE TABLETS

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ABSTRACT

The purpose of the present work was to formulate and evaluate orodispersible tablets of salbutamol sulphate using novel superdisintegrants, exhibiting adequate mechanical strength and disintegration time. The orodispersible tablets were formulated using a novel superdisintegrants (chitosan-alginate (1:1) interpolymeric complex, chitin) and glycine in different concentration ratios. The result revealed that chitin (10-20%) increases porosity and decreases the DT of the tablets with tablet crushing strength 4.25 kg/cm^2. Further, disintegration of tablet is achieved within fraction of second due to swelling of chitosan- alginate complex by glycine transported aqueous medium to different parts of the tablets. Tablet were evaluated to weight variation, hardness, friability, wetting time, disintegration time, drug content, in-vitro drug release and short term stability studies. The present study indicated that excipients used in formulation not only improved the disintegration time and drug release but also to formulate ODTs with higher crushing strength.

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Keywords:- *orodispersible tablets, glycine, chitosan-alginate complex, chitin, salbutamol sulphate.*

INTRODUCTION

Orodispersible drug delivery system, are the solid dosage forms which disintegrate or dissolve within 1 minute when placed in the mouth without the need of water or chewing. Nowadays ODTs were popular and convenient for geriatric, paediatric, bed-ridden and travelling patients. The basic aim is to develop a newer disintegrating system, using highly water soluble excipients in the formulation with higher mechanical strength of the tablet. The present study was to develop and characterize a water soluble excipients such as biodegradable polymers (like chitosan-alginate, chitin), glycine and spray dried lactose which possess all the basic requirements of orodispersible tablets in terms of easy availability, good mouth feel, cost effectiveness, sufficient mechanical strength, non grittiness in the mouth and rapid disintegration time.

The tablets were prepared by direct compression method which was inexpensive, simple and produces tablets with sufficient

mechanical integrity in terms of improved oral absorption, faster onset of action, improved bioavailability. Were, chitosan-alginate complex, chitin and glycine as model excipients for its superdisintegrant properties as possessing sufficient mechanical strengths without the use of complicated unit operations.

Chitin is a natural polysaccharide obtained from crab and shrimp shells and chitosan is obtained by deacetylation of chitin. Chitin possesses amino group covalently linked to acetyl group as compared to free amino group in chitosan. Chitin though has been reported to be used for its disintegration properties in conventional dosage forms but its novel use as a combination containing chitosan-alginate complex, chitin and glycine for good mouth feel disintegrating system. The main objective of the research work was to evaluate and optimize the superdisintegrant properties of chitin and chitosan-alginate complex.

Salbutamol sulphate is a β_2 –adrenoceptor agonist used in the treatment of asthma. It is administered orally in a dose of 2 to 4 mg. rapid action of salbutamol sulphate is not achieved by administering it in conventional dosage forms. In addition, swallowing conventional tablets requires considerable quantity of water, which is often difficult for patient suffering from sudden episodes of allergic attacks or coughing and unavailability of water. Hence, orodispersible tablets of salbutamol sulphate provide distinct advantages over its conventional tablet dosage forms.

From the above, the present study was aimed to evaluate the role of various combinations containing chitosan-alginate complex, chitin and glycine in orodispersible tablets of salbutamol sulphate and formulate ODTs by using novel superdisintegrants without compromised tablet properties.

MATERIALS AND METHOD

Materials

Materials used in this study were obtained from various sources. Salbutamol Sulphate (Apex healthcare limited, Gujarat, India) were, received as a gift sample. chitosan, chitin, glycine and sodium alginate (Research lab fine chemical industries, Mumbai, India) and spray dried lactose.(Wochkrdt Research Center, Aurangabad, India) All other reagents were of analytical grade.

Method

Preparation of chitosan-alginate complex (CTN-ALG complex)

The CTN-ALG was prepared by coacervation-phase separation method. Chitosan solution was prepared by dissolving chitosan (5.0%w/v) in 20 ml of 2%v/v acetic acid. Separately, a solution of sodium alginate (5.0% w/v) in 20 ml distilled water was prepared. Chitosan solution was added to alginate solution dropwise with constant stirring (250 rpm). Isopropyl alcohol was then added to completely separate chitosan-alginate interpolymeric complex. The washed CTN-ALG was dried in an oven (50°C, 12 hr) and then sieved (#22) to obtain uniform size powder.

Formulation of salbutamol sulphate ODTs by direct compression method

The effect of selected active process and concentration (table 1) on disintegration time (DT), wetting time (WT), in vitro dissolution studies was screened. That were, found to be significantly influence the DT, WT and cumulative % drug release during initial screening studies. All the ODTs were prepared by the following method. Glycine (50%w/w), chitin (10-20%w/w) and CTN-ALG complex (5-15%w/w) were mixed in dry state. To this mixture, spray dried lactose (11-44%w/w) and salbutamol sulphate (4%w/w) were added and blended by tumbling. The resulting blend was compressed into tablets with a multipunch eight station rotary tablet machine (Cadmach) by direct compression. The average weight and diameter of round shaped ODTs was 100±5 mg and 7±0.5 mm, respectively. (Table no. 1)

EVALUATION OF POWDER BLEND

The prepared blend is evaluated by following tests:

- Bulk density
- Tapped density
- Hausner’s ratio

- Compressibility index
- Angle of repose

Bulk Density (Db):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$Db = M / Vb$$

Where, M- is the mass of powder.

Vb - is the bulk volume of the powder (ml).

Tapped Density (Dt):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 100 times and the tapped volume was noted. It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M- is the mass of powder (gm).

Vt - is the tapped volume of the powder.

Hausner's ratio:

Hausner ratio is an indirect index of ease of powder flow. It is determined by the following formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density.

Db is the bulk density.

Compressibility index:

It indicates powder flow properties. It is expressed in percentage and is given by,

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt is the tapped density of the powder

Db is the bulk density of the powder.

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

$$\tan(\theta) = h / r$$

$$(\theta) = \tan^{-1}(h / r)$$

Where, (θ) is the angle of repose

h is the height in (cm)

r is the radius in (cm).

Evaluation of ODTs

Weight variation:

The weight variation test was carried out in order to ensure the uniformity of weight in a batch. 20 tablets were selected randomly from each formulation and weighed individually.

Hardness:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Wetting time (WT):

Five circular pieces of tissue paper (10 cm diameter) were placed in a Petri dish and 10 ml water was added. A tablet was carefully placed on the surface of the tissue paper. The time required for the water to appear on the upper surface of the tablet was noted.

In vitro disintegration time (DT):

The in vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specification. Place on tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±2°c as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute. The time in seconds taken for complete disintegration of tablet with no palpable mass remaining in the apparatus was measured and recorded.

Friability:

The friability of the tablet was measured using Roche friabilator. For tablet with an average weight 0.65 gm or less take a sample of whole tablets corresponding to about 6.5 gm and for tablets with an average weight of more than 0.65 gm take a sample of 10 whole tablets. Dedust and weigh accurately the required number of tablets. Place the tablets in the drum and rotate them 100 times.

The tablets were dedust and weighed again. The percentage friability was measured using formula:

$\% F = \{(W_0 - W_1) / W_0\} \times 100$

Where, % F = friability in percentage

W_0 = initial weight of tablets

W_1 = final weight of tablets

Content uniformity:

Four tablets were weighed and powdered. Then weighed powder contain equivalent to 4 mg of drug was taken and transferred into a 100 ml volumetric flask containing 25 ml PH 6.8 phosphate buffer. The drug was allowed to dissolve in the solvent and sufficient quantity of pH 6.8 phosphate buffer was added up to the mark. After few minute the solution was filtered, and take 5 ml from above solution were diluted up to 10 ml with pH 6.8 phosphate buffer. Prepared solution was analyzed at wavelength 277 nm using UV spectrophotometer. The amount of salbutamol sulphate was estimated by using standard calibration curve of drug.

In vitro release studies:

The amount of salbutamol sulphate released from ODTs was evaluated by using USP dissolution apparatus II – paddle using 900 ml of pH 6.8 phosphate buffer as dissolution medium at 37±0.5°c and stirring speed of 50 rpm. 10 ml volume withdrawn at different time intervals were immediately filtered through 0.45 micron membrane filter and analyzed by using UV spectrophotometer at 277 nm. The concentration of the drug was determined from standard calibration curve.

Stability studies:

In the present study, stability studies were carried out at 40±2°c/75%±5%RH for specific time period up to 3 months for selected formulation.

RESULTS AND DISCUSSION

Preliminary trials were taken, that produced a significant effect on DT, WT and cumulative % drug release, are shown in Table no. 2. The results revealed that all these dependent parameters were significantly influenced by concentration of glycine, CTN-ALG complex and chitin. The DT and WT of ODTs containing 50% w/w of glycine, 10% w/w of CTN-ALG complex, and 15% w/w of chitin were lower than those of ODTs containing other concentration.

Further, all the formulations were subjected for pre-compression and post compression evaluation. The various pre-compression parameters, like bulk density, tapped density, hausner's ratio, compressibility index, angle of repose were measured to evaluate powder blend.(Table no.3) It was found that excellent flow properties and can be used for tablet manufacturing.

Post compression parameter-

The tablets were prepared by direct compression method. Various physical parameter like, weight variation, hardness, friability, disintegration time, wetting time, content uniformity, were measured to evaluate tablets. All The formulated tablets showed satisfactory disintegration time, wetting time and other physical parameters like weight variation, hardness, friability and content uniformity. (Table no. 4)

In vitro dissolution studies shows, satisfactory drug release with the combination of novel superdisintegrants in all batches. Drug release curve shows the fast drug release from all the batches of ODTs of salbutamol sulphate. (Figure no. 1) Amongst all the batches F5 has shows satisfactory and fast drug release with 97.33% and rapidly wetted, disintegrated in the oral cavity even when prepared at tablet crushing strength more than 3.5 kg/cm^2 Hence, batch F5 has selected as a optimized batch for ODTs of salbutamol sulphate. (Table no. 5)

Stability studies:

The stability studies revealed that the formulation was physically stable when stored at 40±2°c and 75±5% RH till 3 months and there has no significant differences in hardness, friability, disintegration time, wetting time, drug content and cumulative % drug release for optimized formulation. (Table no. 6)

CONCLUSION

From the investigation, it can be demonstrate that it is possible to develop ODTs with chitosan-alginate complex and chitin as a natural

polysaccharide shows the significant configuration in the different ratios in combination rather than their individual contribution. Chitin was found to function as an excellent tablet hardness promoter at a concentration higher than 10% w/w. A combination of chitosan-alginate complex (10%w/w), chitin (15%w/w) and glycine (50%w/w) was found to have superdisintegrant activity. This combination was found to be the optimum for formulating ODTs even at tablet crushing strength of 4.25 kg/cm^2. So that batch F5 has optimized formulation in this study. Short term stability studies of optimized formulation F5 indicate that there are no significant changes in dosage form when changing temperature, relative humidity in three months.

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Table no. 1. Formulation of ODTs using novel superdisintegrants

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Salbutamol sulphate	4	4	4	4	4	4	4	4	4
Glycine	50	50	50	50	50	50	50	50	50
CTN-ALG complex	5	5	5	10	10	10	15	15	15
Chitin	10	15	20	10	15	20	10	15	20
Spray dried lactose	31	26	21	26	21	16	21	16	11
Total	100	100	100	100	100	100	100	100	100

Table no. 2. Preliminary trials formulation and process parameter influencing DT, WT and Cumulative % drug release.

Batch no.	Glycine (%w/w)	CTN-ALG (%w/w)	Chitin (%w/w)	DT (sec)	WT(sec)	Cumulative % drug release (%)
F1	50	5	10	31.66±1.5	37.66 ± 2.5	92.95±0.22
F2	50	5	15	29.00±0.5	34.00 ± 2.5	93.07±0.21
F3	50	5	20	26.33±0.5	30.33 ± 2.5	96.09±0.21
F4	50	10	10	30.33±1.5	29.66 ± 0.5	93.16±0.18
F5	50	10	15	24.00±1.0	25.66 ± 1.5	97.33±0.25
F6	50	10	20	27.00±1.0	27.33 ± 1.5	94.03±0.25
F7	50	15	10	28.60±1.0	29.33 ± 1.1	93.13±0.24
F8	50	15	15	27.33±2.0	25.66 ± 0.5	96.09±0.29
F9	50	15	20	27.00±1.0	27.66 ± 1.5	94.38±0.22

CTN-ALG = chitosan- alginate complex; DT = disintegration time; WT = wetting time.

Table no. 3. Pre-compression parameter of powder blend

Batch no.	Bulk density (gm/ml)	Tapped density(gm/ml)	Hausner's ratio	Compressibility index (%)	Angle of repose
F1	0.332±0.05	0.384±0.07	1.15±0.04	13.43±0.2	24.13±0.10
F2	0.340±0.08	0.397±0.08	1.16±0.01	14.25±0.5	23.89±0.19
F3	0.350±0.06	0.408±0.05	1.17±0.03	14.13±0.1	25.43±0.17

F4	0.336±0.08	0.387±0.09	1.14±0.07	13.09±0.7	23.35±0.06
F5	0.340±0.08	0.397±0.09	1.16±0.04	14.25±0.5	22.89±0.13
F6	0.335±0.02	0.392±0.02	1.15±0.03	13.68±0.3	24.28±0.11
F7	0.334±0.09	0.389±0.06	1.14±0.01	12.92±0.5	23.39±0.15
F8	0.337±0.07	0.384±0.07	1.14±0.01	13.09±0.7	23.48±0.09
F9	0.348±0.09	0.405±0.09	1.15±0.05	14.05±0.2	24.40±0.11

Table no. 4. Post compression parameter of formulated tablets

Batch no.	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	WT (sec)	DT (sec)	Drug content (%)
F1	4.10±0.25	98.00±1.45	0.64±0.12	38.00±1.78	31.84±1.60	99.17±0.72
F2	4.25±0.27	97.95±1.34	0.66±0.14	33.84±1.83	29.76±1.47	98.58±1.47
F3	4.16±0.25	98.40±1.31	0.57±0.20	30.16±1.60	26.85±1.00	99.02±1.08
F4	4.08±0.20	98.10±1.25	0.69±0.19	28.50±1.64	30.00±1.00	99.02±1.45
F5	4.25±0.27	98.53±1.34	0.49±0.21	25.83±1.16	23.66±1.21	99.03±0.92
F6	4.16±0.23	97.95±1.31	0.58±0.17	28.00±1.23	26.68±1.22	98.73±1.34
F7	4.08±0.21	99.05±1.05	0.72±0.09	29.33±1.21	28.50±1.37	99.06±1.21
F8	4.25±0.27	97.63±1.53	0.74±0.13	27.40±0.9	27.00±1.89	100.35±0.45
F9	4.10±0.25	98.26±1.36	0.66±0.12	27.85±1.16	27.85±1.16	98.58±1.47

***In vitro* dissolution studies:**

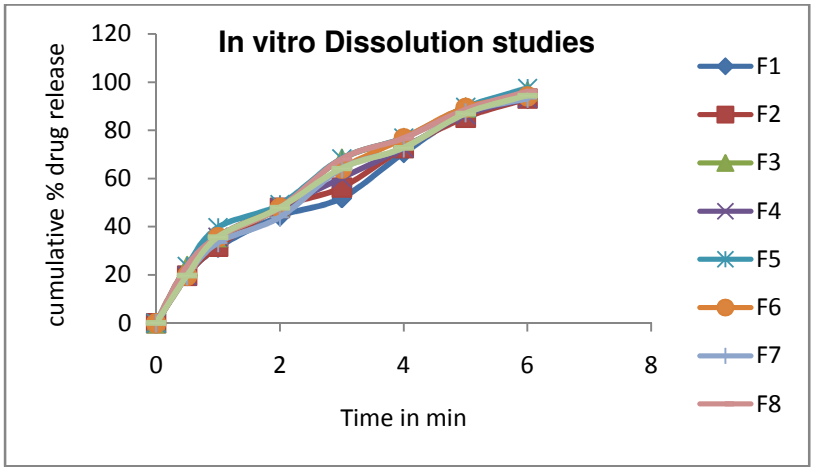
Table no. 5. *In vitro* dissolution studies of ODTs of salbutamol sulphate in pH 6.8 phosphate buffer.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	19.69± 0.22	19.69± 0.73	23.63± 0.13	19.69± 0.22	23.63± 0.42	19.69± 0.23	19.69± 0.33	23.63± 0.39	19.69± 0.52
1	31.32± 0.45	31.72± 0.04	35.70± 0.45	35.66± 0.40	39.64± 0.23	35.66± 0.31	33.30± 0.39	35.70± 0.23	35.66± 0.22
2	44.27± 0.22	47.82± 0.27	47.91± 0.22	47.87± 0.35	49.14± 0.32	47.87± 0.36	43.90± 0.40	47.91± 0.44	47.87± 0.28
3	51.85± 0.18	56.23± 0.20	68.13± 0.32	60.21± 0.15	68.19± 0.56	64.15± 0.21	64.08± 0.24	68.13± 0.21	64.15± 0.39
4	70.53± 0.40	72.59± 0.28	76.75± .18	72.68± 0.23	76.81± 0.67	76.66± 0.27	72.65± 0.05	76.75± 0.22	72.72± 0.33
5	86.65± 0.45	85.20± .13	89.40± 0.13	86.46± 0.23	89.45± 0.45	89.31± 0.07	87.23± 0.22	88.61± 0.25	86.90± 0.39
6	92.95± 0.22	93.07± 0.21	96.09± 0.21	93.16± 0.18	97.33± 0.25	94.03± 0.25	93.13± 0.24	96.09± 0.29	94.38± 0.22

Table no. 6. Stability data for optimized formulation F5

Formulation	Parameters	Time interval (months)			
		0	**1**	**2**	**3**
F5	**Hardness (kg/cm^2)**	**4.0**	**4.5**	**4.5**	**4.0**
	Disintegration time (sec)	24	22	23	24
	Wetting time (sec)	27	26	27	27

	Friability (%)				
	Drug content (%)	0.5	0.67	0.49	0.67
	Cumulative % drug release				
		98.58	99.47	99.02	99.47
		97.34	97.33	96.98	97.33



- **Figure no. 1. In vitro dissolution studies of ODTs of salbutamol sulphate in pH 6.8 phosphate buffer**

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