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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF SALBUTAMOL FLOATING TABLETS BY USING VARIOUS POLYMERS

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ABSTRACT

The objective of our work is to formulate a sustained release dosage form of Salbutamol by using floating drug delivery technology. Floating tablets has been useful for sustain or controlled release of drug. Under the present work we have planned to formulate a floating drug delivery system using different polymers & its evaluation studies were carried out.

From the 10 formulations we found that the formulation containing carbopol (F7&F9) were showed the better sustain release when compared to the other formulations. The floating time of formulation range from 8.15 to 12 hrs has and the Swelling Index of different formulations range from 1.78 to 16.15.

Hence it can be concluded from the present study that Salbutamol is an ideal drug for formulation as sustain release product. Floating drug delivery system have the property of retaining the dosage units in the stomach for prolonged period of time, and these systems increase the safety of a product to extend the side effects of drugs.

INTRODUCTION

Historically speaking, oral drug administration has been the predominant route for drug delivery due to the ease of administration, patient convenience, and flexibility informulations. However, it is a well-accepted fact today that drug absorption throughout the gastro-intestine tract is not uniform .Using current release technology, oral drug delivery for 12 or 24hours is possible for many drugs that are absorbed uniformly from the GI tract. Nevertheless this approach is not suitable for a variety of important drugs characterized by a narrow absorption window in the upper tract of the GI Tract, i.e., stomach and small intestine. To overcome these problems and improve the efficacy of oral administration, some recent studies have reported that controlled oral drug delivery systems with prolonged gastric residence time, have been proved to be advantageous. Floating drug delivery is one such system this review gives the basic concept and research trends to achieve controlled release with prolonged gastric residence through fabrication of the floating drug delivery (Lachman *et al*, 1986, Yie W. Chien -1992).

The principal mechanism of floatation is to achieve gastric retention. Gastro-retentive dosage forms are primarily controlled release drug delivery systems, which get retained in the stomach for longer periods of time, thus helping in absorption of the drug for the intended duration of time. Gastric-retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs. Gastro- retentive dosage forms will also greatly improve the pharmacotherapy of the stomach itself through local drug release, leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time. Finally, gastro-retentive dosage forms will be used as carriers for drugs with so called absorption window: these substances are taken up only from very specific sites of the gastrointestinal mucosa, often in a proximal region of the small intestine (Howard C. Ansel *et al,* 1995).

Salbutamol sulfate is usually given by the inhaled route for direct effect on bronchial smooth muscle. This is usually achieved through a metered dose inhaler (MDI), nebulizer or other proprietary delivery devices (e.g. Rotahaler or Autohaler). In these forms of delivery, the maximal effect of Salbutamol can take place within five to twenty minutes of dosing, though some relief is immediately seen. Salbutamol can also be given orally as an inhalant or intravenously.

Salbutamol which is a short acting beta adrenergic receptor agonists used for the relief of bronchospasm in condition such as asthma and chronic obstructive pulmonary disease. Salbutamol binds to β2 adrenergic receptors with a higher affinity than β1 receptor. Result in relaxation of bronchial smooth muscle.

As a β2-agonist, Salbutamol also finds use in obstetrics. Intravenous Salbutamol can be used as a tocolytic to relax the

uterine smooth muscle to delay premature labor. While preferred over agents such as atosiban and ritodrine, its role has largely been replaced by the calcium-channel blocker nifedipine which is more effective, better tolerated and orally administered.[2]

In an emergency, EMS providers consider the administration of Albuterol when they see Active Wheezing, bronchospasm and a past diagnosis of Asthma. The drug is most often administered through a nebulizer with 8 liters of pure oxygen. A normal dose is aprox. 2.5 mg in 3 mL of respiratory saline. The objective of our work is to formulate a sustained release dosage form of Salbutamol by using floating drug delivery technology. Floating tablets has been useful for sustain or controlled release of drug. Under the present work we have planned to formulate a floating drug delivery system using different polymers & its evaluation studies were carried out (DrugBank).

Material

Following are the list of materials used for formulation of floating tablet of Salbutamol sulphate

Table 1 List of Ingredient's with functional category

S.no	Ingredients	Function
1.	Salbutamol Sulphate	Active Drug
2.	Hydroxypropyl Methyl cellulose (HPMC)	Extend release tablet matrix/binder
3.	Microcrystalline Cellulose (MCC)	Diluent and disintegrant
4.	Sodium Bicarbonate ($NaHCO_3$)	Gas forming agent
5.	Sodium Alginate	Binder and disintegrant
6.	Carbopol	Rate controlling excipient/binder
7.	Citric Acid	Diluents
8.	Polyethylene Glycol (PEG) 6000	Lubricant and coating agent
9.	Poly Vinyl Alcohol	Lubricant and coating agent
10.	Shell Lac	Binder
11.	Tartaric Acid	Diluent
12.	Sodium Carboxymethyl Cellulose	Binder and disintegrant
13.	Cetyl Alcohol	Coating agent and stiffing agent
14.	Dextrin	Diluent/binder
15.	Starch	Binder /diluent/disintegrant
16.	Lactose	Diluent
17.	Talc	Dissolution retardant
18.	MagnesiumStearate	Lubricant

METHODS

Procedure for Formulation of F1 to F7 trial: Salbutamol, HPMC/Na CMC/HPMC, Na CMC/HPMC,PEG were respectively passed through sieve no.30 and mixed thoroughly.6000/HPMC, Sodium alginate/MCC,NaHCO3/ Carbopol, Sodium alginate and Starch. were added. Then tablets were prepared by direct compression method with an avg wt of 500mg using 16 station punching machine. The amounts of ingredients used were tabulated in table 2.

Procedure for Formulation of F8 to F9: First Salbutamol is complexes with dextrin in both the formulation. Separately the polymer HPMC, NaHCO3, Cetyl -alcohol/carbopol, sodium alginate were mixed respectively for F8 and F9.Then taken the Salbutamol-dextrin complex, and mixed with HPMC, NaHCO3, Cetyl alcohol /carbopol, sodium alginate mixture then starch is also mixed. Then the mixture was passed through sieve no.30 after making into a fine powder. To it lactose was added and mixed thoroughly. Finally lubricants i.e.,talc and mg stearate were added in mentioned ratio. Then tablets were prepared by direct compression with an avg wt of 500mg using 16 station punching machine. The amounts of ingredients required were tabulated in table 2.

Procedure for Formulation of F10: In this formulation first NaHCO3 was mixed with tartaric acid, then to it Salbutamol was added. Then separately taken shell lac and into a fine powder and to it polyvinyl alcohol was added and mixed well. Then added to the above mixture. Then starch was added and the total mixture was passed through sieve no.30 and then lactose was added to the powder. Finally talc and Mg state was added to it in mentioned ratio. Then the tablets were prepared by direct compression with avg wt of 500mg using 16 station punching machine.

Evaluation of Hydrodyamically balanced Tablets Salbutamol sulphate

Pre-compression Parameter

1. Angle of Repose: The values obtained for angle of repose for all formulations were found to be in the range from 240.30' to 290.88'. This indicates good flow property of the powder blend for direct compression.
2. Compressibility index: The values obtained for Compressibility index for all formulations were ranges between 12.30% to 16.34% indicating that the powder blend have the required flow property for direct compression.

Table 2 Formulation Trials

S.NO	INGREDIENTS	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1.	Salbutamol	20	20	20	20	20	20	20	20	20	20
2.	HPMC	100	-	125	200	200	-	-	100	130	-
3.	Na CMC	-	250	125	-	-	-	-	-	-	-
4.	PEG 6000	-	-	-	50	-	-	-	-	-	-
5.	Sodium Alginate	-	-	-	-	50	-	50	-	-	-
6.	MCC	150	-	-	-	-	200	-	-	-	-
7.	$NaHCO_3$	-	-	-	-	-	50	-	50	65	50
8.	Carbopol	-	-	-	-	-	-	200	-	-	-
9.	Dextrin	-	-	-	-	-	-	-	20	20	-
10.	Cetyl Alcohol	-	-	-	-	-	-	-	80	-	
11.	Polyvinyl Alcohol	-	-	-	-	-	-	-	-	-	75
12.	Citric Acid	-	-	-	-	-	-	-	-	35	-
13.	Tartaric Acid	-	-	-	-	-	-	-	-	-	50
14.	Shell Lac	-	-	-	-	-	-	-	-	-	75
15.	Maize Starch	50	50	50	50	50	50	50	50	50	50
16.	Lactose	150	150	150	150	150	150	150	150	150	150
17.	Talc	25	25	25	25	25	25	25	25	25	25
18.	Magnesium Sterate	5	5	5	5	5	5	5	5	5	5
	Tablet Weight	500	500	500	500	500	500	500	500	500	500

*TOTAL=500mg *all ingredients in mg units

1. Shape of the Tablet: The examination of tablets from each formulation batch showed circular shape with no cracks.
2. Tablet Dimensions: The dimensions determined for formulated tablets were almost uniform in all the ten formulations and were found to be in the range of 5.12 mm to 5.18 mm. The diameter of the tablet ranges between 10.90 mm to 11.10 mm.
3. Hardness Test: The measured hardness of tablets of each batch ranged between 4.1 to 4.5 kg/cm2
4. Friability Test: The values of friability test were less than 1% in all the formulations ensuring that the tablets were mechanically stable.
5. Weight variation test: The percentage weight variations for all formulations were within the Pharmacopoeial limits of □5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.
6. Tablet Density: To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (1.004g/cm3). All the batches showed density below than that of gastric fluid (1.004).
7. Buoyancy Study: On immersion in 0.1N HCl solution pH (1.2) at 37^0C, the tablets floated, and remained buoyant without disintegration. From the results it can be concluded that the batch containing HPMC polymers showed good buoyancy lag time (BLT) and total floating time (TFT). Formulation F10 containing HPMC K15M, HPMC K100M and Carbopol Ca934P showed good BLT of 110 sec and TFT of more than 24 hrs. Carbopol was used as release retardant and it also provided an additional gelatinous layer to the formulation. The tablets floats may be due to the amount of polymer and gas generating agents, which gets partially entrapped in between, the gelatinous layer.
8. Drug content uniformity: The percentage of drug content was found to be between 97.01% and 99.82% of Salbutamol, which was within acceptable limits.
9. Swelling index: This is determined by width of the tablet. By using the formula the swelling index can be determined.

SI = (width after 8hr)-(initial width of tab) x 100
Initial width of tablet
SI = (diameter after 8hr)-(initial diameter of tab) x 100
Initial diameter of tablet

Dissolution

400ml of 0.1N Hcl was taken in a beaker and Teflon was placed in it. Then one tablet was taken and placed into it. The rpm of stirrer was set at 50 rpm and temperature 370+20c. After 1hr 7ml of dissolution medium was collected. The medium was again replaced with 0.1N Hcl. The samples were collected at every 1hr interval up to 8hr. To the collected samples 1ml of 3%sodium nitrate,1ml of copper sulphate and 0.2ml of 1N Hcl were added. Then it was warmed on a water bath for 10min and cooled to room temperature. Then the final volume is made up to 10 ml with 0.1N Hcl. After 25 min the absorbance was measured at 525 nm against blank.

RESULTS AND DISCUSSION

This work describes the formulation and evaluation of Salbutamol floating tablets. Ten different batches of floating tablets were prepared by using different polymers like HPMC, NaCMC, Carbopol and other polymers.

Table 3 Results of Angle of repose and compressibility index

S.no	Formulation code	Angle of repose	Compressibility index(%)
1	F_1	$24^0.30'$	12.30
2	F_2	$26^0.77'$	15.67
3	F_3	$25^0.77'$	16.34
4	F_4	$28^0.56'$	15.41
5	F_5	$29^0.88'$	13.25
6	F_6	$24^0.36'$	14.16
7	F_7	$25^0.22'$	12.45
8	F_8	$27^0.29'$	15.56
9	F_9	$26^0.54'$	14.48
10	F_{10}	$28^0.48'$	14.85

Table 4 Results of physical properties of tablets

S.No	Formulation code	Diameter	Thickness	Hardness	Friability	Weight variation
1.	F_1	13.58	4.032	2.6	0.5	Passes I.P Limits
2.	F_2	13.54	4.030	3.2	0.3	Passes I.P Limits
3.	F_3	13.50	4.025	3.4	0.3	Passes I.P Limits
4.	F_4	13.58	4.032	2.6	0.4	Passes I.P Limits
5.	F_5	13.60	4.034	3.0	0.4	Passes I.P Limits
6.	F_6	13.54	4.030	3.0	0.5	Passes I.P Limits
7.	F_7	13.50	4.025	3.8	0.3	Passes I.P Limits
8.	F_8	13.52	4.027	3.4	0.2	Passes I.P Limits
9.	F_9	13.58	4.032	3.6	0.4	Passes I.P Limits
10.	F_{10}	13.54	4.030	3.4	0.4	Passes I.P Limits

Table 5 Floating time

Formulation Code	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Floating Time (hrs)	12	10	10.3	12	11	10.45	14	9	12.3	8.15

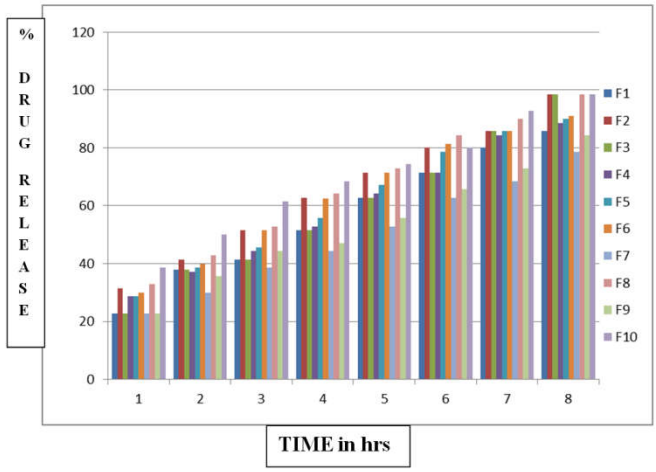
Table 6 Swelling Index

S.No	Formulationcode	Swelling Index	
		Thickness	Diameter
1.	F_1	34.42	08.54
2.	F_2	26.05	03.84
3.	F_3	15.77	01.78
4.	F_4	30.95	06.04
5.	F_5	27.42	03.82
6.	F_6	16.63	02.81
7.	F_7	55.03	16.15
8.	F_8	12.74	04.44
9.	F_9	44.84	13.55
10.	F_{10}	16.13	04.87

Table 7 Percentage Drug Release in Different formulations

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	22.85	31.4	22.85	28.6	28.6	30	22.85	32.85	22.85	38.55
2	38	41.45	38	37.15	38.55	40	30	42.85	35.7	50
3	41.45	51.45	41.45	44.3	45.7	51.45	38.55	52.85	44.3	61.4
4	51.45	62.85	51.45	52.85	55.7	62.85	44.3	64.3	47.15	68.55
5	62.85	71.45	62.85	64.3	67.15	71.45	52.85	72.85	55.7	74.3
6	71.45	80	71.45	71.45	78.55	81.45	62.85	84.3	65.7	80
7	80	85.7	80	84.3	85.7	85.7	68.55	90	72.85	92.85
8	85	98.55	85	88.55	90	91.14	78.55	98	84.3	98.55

Comparision of Invitro Release of Salbutamol Floating Tablets



SUMMARY AND CONCLUSION

Novel drug delivery systems are becoming one of the most important fields in the modern pharmaceutical formulation technology. several techniques are employed to design the sustained and controlled drug delivery system.

In the present study an attempt has been made to develop sustain drug delivery systems by formulating floating tablets using various polymers. The drug chosen for this study is Salbutamol which is a short acting beta adrenergic receptor agonists used for the relief of bronchospasm in condition such as asthma and chronic obstructive pulmonary disease. Salbutamol binds to β2 adrenergic receptors with a higher affinity than β1 receptor. Result in relaxation of bronchial smooth muscle.

Floating tablets can be retained in the stomach for long time it is important for drugs that are degraded in intestine. Drugs are poorly soluble in intestine due to alkaline pH and then its retention in gastric region may increase the solubility before emptied and prolongs overall gastric intestine transition time, increased bio-availability. Floating tablets were prepared by mixing various polymers and find out the most suitable and successful type of polymer formulation.

The floating time of formulation range from 8.15 to 12 hrs and the Swelling Index of different formulations range from 1.78 to 16.15. Formulation 1 showed a release of about 22%at the first hour and almost complete release at end of 8 hrs. Formulation 2 &3 showed a release about 31% and complete release at end of 8 hrs. Formulation 4&5 showed a release about 28% and complete release at end of 8 hrs. Formulation 6 showed a release about 30% and complete release at end of 8 hrs. Formulation 7&9 showed a release about 22% and only around 80% release at end of 8 hrs. Formulation 8 &10 showed a release about more than 32% approximately and around near 90% release at end of 7 hrs. From the 10 formulations we found that the formulation containing carbopol (F7&F9) were showed the better sustain release when compared to the other formulations.

Ichikawa et al developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/mL. It was found that the system had good floating ability independent of pH and viscosity and the drug (para-amino benzoic acid) released in a sustained manner (Ichikawa *et al*, 1991.

Nur and Zhang developed floating tablets of captopril using HPMC (4000 and 15 000 cps) and carbopol 934P. In vitro buoyancy studies revealed that tablets of 2 kg/cm2 hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm2 sank for 3 to 4 minutes and then came to the surface. Tablets in both cases remained floating for 24 hours. The tablet with 8 kg/cm2 hardness showed no floating capability. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the center of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved (7.Nur AO *et al*, 2000).

Yang et al developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori–associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Hydroxypropylmethylcellulose and poly(ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporatinga gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The in vitro results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. The floating feature aided in prolonging the gastric residence time of this system to maintain high-localized concentration of tetracycline and metronidazole (Yang J-C., *et al,*2014)

Li et al evaluated the contribution of formulation variables on the floating properties of a gastro floating drug delivery system using a continuous floating monitoring device and statistical experimental design. The formulation was conceived using taguchi design. HPMC was used as a low-density polymer and citric acid was incorporated for gas generation. Analysis of variance (ANOVA) test on the results from these experimental designs demonstrated that the hydrophobic agent magnesium stearate could significantly improve the floating capacity of the delivery system. High-viscosity polymers had good effect on floating properties. The residual floating force values of the different grades of HPMC were in the order K4 M~ E4 M~K100 LV> E5 LV but different polymers with same viscosity, i.e., HPMC K4M, HPMC E4M did not show any

significant effect on floating property. Better floating was achieved at a higher HPMC/carbopol ratio and this result demonstrated that carbopol has a negative effect on the floating behavior (Li S, *et al,* 2013).

CONCLUSION

Hence from the above data it can be concluded that Salbutamol is an ideal drug for formulation as sustain release product. Currently these are a number of control release preparations of Salbutamol in the market. Floating drug delivery system have the property of retaining the dosage units in the stomach for prolonged period of time, and these systems increase the safety of a product to extend the side effects of drugs .sustain release/ control release Salbutamol floating tablets are most useful in the various treatment of long term therapy.

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