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Gastroretentive Drug Delivery System of Levo-Salbutamol Sulphate: Formulation and *in vitro* Evaluation

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ABSTRACT

In order to prepare the sustained release tablet with levo-salbutamol sulphate we have used these excipients methylcellulose, PVPK30, magnesium stearate, talc, isopropyl alcohol, microcrystalline cellulose, lactose, HPMCK100, HPMCK4M. Here our approach was for making the sustained released matrix tablet by two ways, one is to make the tablet granules floating and the second one is by retarding the release of the levo-salbutamol sulphate from the matrix. We have already discussed the relationship with delaying the gastric transit time and the active drug absorption, if the tablet granules are floating in our introduction part. Since the above mentioned excipients are floating in nature so formulations with those excipients are supposed to be floating. We also showed a list of excipients those are used in the preparation of floating tablets. Now the second observation which was the release rate, among the three different formulations (mentioned in the introduction) we found different types of release. Since our objective is to prepare a sustained released tablet which will give a prolong release time, in that prospect two among the three formulations were disqualified (though we have not done the kinetic study). We observed desired effect in the formulation-2 during the preparation of experiment.

Keywords: Gastroretentive, Levo-salbutamol sulphate, Buoyancy.

INTRODUCTION

Levo-salbutamol sulphate is one of the widely used drugs for the treatment of bronchial asthma, chronic bronchitis and emphysema. [1] The drug undergoes extensive first-pass metabolism and thus requires frequent administrations by oral route. [2] Levo-salbutamol sulphate has a site-specific absorption in stomach and upper part of small intestine. [3] Reported oral bioavailability of levo-salbutamol sulphate is ~ 40%; due to extensive metabolism via intestinal sulphonation, first pass metabolism in liver & also degradation in colon. [4] The metabolism is due to extensive sulphonation in gut as compared to liver. [5] The half life of levo-salbutamol sulphate is about 4.5 hours. [6] The relatively short term acting injectables and aerosol dosage forms of levo-salbutamol sulphate are recommended for instant relief in severe asthmatic attacks. Levo-salbutamol sulphate is available in the form of aerosols. The recommended dose in adults and children is 2-3 inhalations every 4-6 h. More frequent administration is not recommended. [7] A gastroretentive drug delivery system may be advantageous over conventional oral dosage forms and inhalers due to its ability to maintain prolonged therapeutic concentrations in the systemic circulation.

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Asthma being a chronic disease, and as most of the patients suffer from nocturnal attacks [8], there is need for drug delivery systems which maintains therapeutic concentrations for long duration. Floating drug delivery systems (FDDS) were first described by Davis in 1968. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. [9] FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine [10], for drugs which act locally in the stomach [11] and for drugs that are poorly soluble or unstable in the intestinal fluid. [12] These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. [13] FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. [14] Based on the mechanism of buoyancy, two distinctly different technologies, *i.e.* non-effervescent and effervescent systems, have been used in the development of FDDS. The effervescent system uses matrices prepared with swellable polymers and effervescent components e.g. sodium bicarbonate and citric acid or stearic acid. In non-effervescent FDDS, the drug mixes with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. [14-15] The aim was to increase bioavailability of levo-salbutamol sulphate and to study the effect of polymer, Citric acid and Stearic acid on drug release profile.

MATERIALS AND METHODS

Levo-salbutamol sulphate and Methylcellulose, HPMC K100M, HPMC K4M, PVP K30, were kind gift from Eskayef Bangladesh Ltd. Microcrystalline cellulose, IPA, were obtained from Primeasia University Laboratory. All ingredients were of analytical grades.

Buoyancy of the polymer used in the floating tablet

Hydrocolloids having maximum buoyancy were selected for formulation of mini floating tablets. Maximum buoyancy was observed in formulations containing HPMC K4M and HPMC (15cps) used alone or in combination with other tablet ingredients as shown in Table 1.

Formulation of floating matrix tablets

Floating matrix tablet were prepared by non effervescent and wet granulation methods using hydrocolloids (Methylcellulose, HPMC K100M, HPMCK4M) as buoyancy agents. The composition of the formulation is given in Table 2. The concentration of the polymer for floating matrix tablet was optimized under experimental formula and condition of the preparation to float in the stomach up to 24 h. The ingredient except glidants and lubricant were thoroughly mixed and passed through sieve no.60. Granulation was done with a solution calculated quantity of PVP K30 (4.8%) in sufficient isopropyl alcohol. The wet mass passed through the sieve no. 10 and dried at 45-55^{o}C for 2 h. The dried granules were sized by sieve no. 22 and mixed with magnesium stearate and, talc. The granules were compressed into tablet on a single paunch tablet machine using 7 mm punch. The tablets were compressed at two different hardness and shape.

Evaluation of different parameters of floating tablets

Pre-compressional Evaluation

Bulk Density Determination

It was expressed in gm/ ml and given by:

$$\text{Bulk Density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

Carr's Consolidation Index

Carr's Index explains flow properties of the granules. It was expressed in percentage and given by:

$$\text{Consolidation Index} = \frac{\text{Tapped Density - Untapped Density}}{\text{Tapped Density}} \times 100$$

Angle of Repose

Angle of repose for prepared granules was determined by fixed funnel method. A funnel was fixed with its tip at a given height h above a flat horizontal surface to which a graph paper was placed. The granules were carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the formula:

$$\text{Angle of Repose } (\theta) = \text{Tan}^{-1} (\text{Height of Pile} / \text{Radius of the base of the pile})$$

Flow rate

The flow rate of the granules was determined by hopper flow rate method, in which time taken for a weighed quantity of granules to flow through an orifice was calculated. It was expressed as gm/sec.

Post-Compressional Evaluation

Thickness and diameter

The thickness and diameter of the tablets were determined by using screw gauze. Thickness of ten tablets was determined randomly. It was expressed in mm.

Crushing strength

The monsanto hardness tester was used to determine the tablet crushing strength. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gave a measure of the hardness of tablet. Hardness was expressed in Kg/cm^2.

Friability

Friability was determined using Roche Friabilator. Twenty tablets were weighed and placed in the friabilator and then operated at 25 rpm for four minutes. The tablets were then dedusted and weighed. It was expressed in percentage. The difference in the two weights is used to calculate friability.

$$\text{Friability} = 100 \times (1 - W/W0)$$

Where, W0 = Initial weight; W = Final weight

Weight Variation Test

Twenty tablets were weighed individually and average weight was calculated. The individual weights were then compared with average weight. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of tablet differs by more than double percentage limit.

$$PD = \frac{W_{avg} - W_{ind}}{W_{avg}} \times 100$$

Where, PD= Percentage Deviation; W_{avg} = Average Weight of Tablet; W_{ind} = Individual Weight of Tablet

Drug Content

Drug content was performed to check dose uniformity in the formulation. Randomly ten tablets were weighed and powdered. A quantity equivalent to 150 mg of levo-salbutamol sulphate was added in to a 100 ml volumetric flask and dissolved in methanol, shaken for 10 minutes and made up the volume up to the mark and filtered. After suitable dilutions the drug content was determined by UV spectrophotometer at 276 nm against blank.

Swelling index of floating tablets

The studies were carried out gravimetrically. Swelling media used for these studies were distilled water and simulated gastric fluid (pH 1.2). The prepared tablets were introduced into the swelling media. At predetermined time intervals the tablets were removed from medium, excess water was blotted with tissue paper and immediately weighed. This procedure was repeated until the tablet reached constant weight. The swelling index was calculated using following formula:

$$\text{Swelling Index} = \frac{W_1 - W_0}{W_0} \times 100$$

Where W_1=Weight of dry tablet; W_0= Weight of swollen tablet

Table 1: Selection of hydrocolloids

S. No.	Polymer	Floating Time (hours)	Buoyancy/Matrix Integrity
1.	MC	6 hours	+++
2.	S C M C	20 hours	+++
3.	HPMC (K4M)	30 hours	++++
4.	HPMC (15cps)	24 hours	++++
5.	EC	3 hours	++
6.	PVP	30 min.	+
7.	HEC	2 hours	+
8.	SMC	4 hours	+++
9.	Sodium Alginate	50 min.	+

++++ = Excellent +++ = Good ++ = Not good + = Poor

Table 2: Formulation of levo-salbutamol sulphate floating matrix tablet

Formulation No.	Drug (Levo-sulbutamol sulphate)	Methyl cellulose	PVP K30-4.8%	Micro-crystaline Cellulose-5%	Lactose	Talc 1%	Magnesium Stearate 1.5%	Isopropyl Alcohol
F-1	16 mg	111.5 mg	7.0 mg	7.5 mg	4.05 mg	1.8 mg	2.15 mg	qs
F-2	16 mg	112.5 mg	7.2 mg	7.5 mg	3.05 mg	1.5 mg	2.25 mg	qs
F-3	16 mg	112.0 mg	7.1 mg	7.6 mg	3.20 mg	1.8 mg	2.25 mg	qs

Total weight of tablets 150 mg

Table 3: Evaluation parameters for levo-salbutamol sulphate floating tablet

S. No.	Parameter
1.	Thickness (mm) 5.87 ± 0.25
2.	Diameter (mm) 8 ± 0.12
3.	Crushing strength(kg/cm2) 2.8 ± 0.59
4.	Friability (%) 0.812 ± 0.48
5.	Average weight (mg) 309.9 ± 0.34
6.	Percent weight variation (%) 2.69 ± 0.75
7.	Drug content (%) 97.10 ± 0.5
8.	Cumulative percent release (%) 85.0 ± 0.85 in 6 hours (pH 1.2 Buffer)

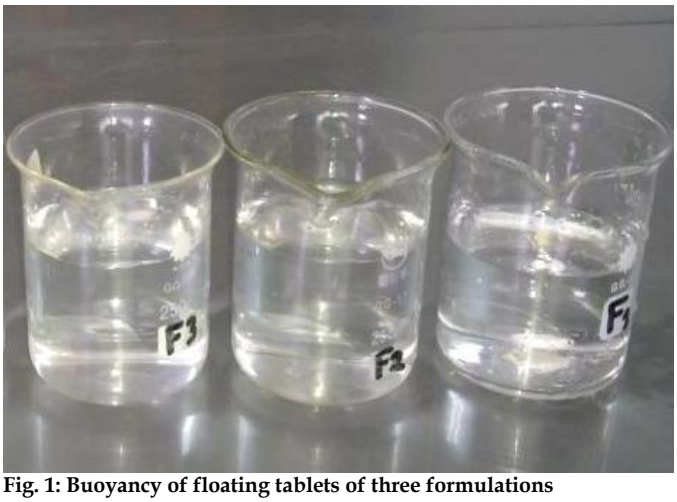

Fig. 1: Buoyancy of floating tablets of three formulations

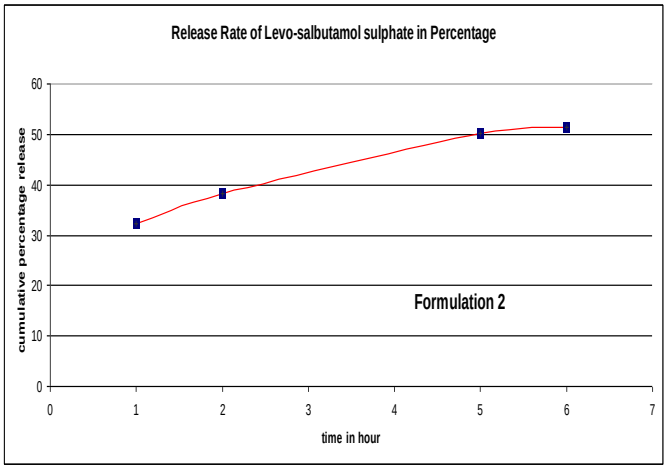

Fig. 2: Graphical representation of sample. Here X-axis represents the time in hour, and in Y-axis represents the cumulative release rate. Here we collected 5 ml sample from the dissolution chamber at different time intervals. Our observation for hourly release at 1st, 2nd, 5th & 6th hour were 32.34%, 38.13 %, 50.10% & 51.36 % respectively.

Buoyancy determination

Floating time were determined using USP tablet dissolution apparatus (VEEGO) at 50 rpm, using 900 mL of 0.1N HCl (stimulated gastric fluid) pH 1.2 and temperature of the medium maintained at 37 ± 0.5°C throughout the study. The duration of the floating time

is the tablet float in the dissolution medium (including buoyancy lag time).

***In vitro* drug release profile**

The drug release was studied using USP Paddle tablet dissolution test apparatus in 900 mL of 0.1 HCl (stimulated gastric fluid) at 37 ± 0.5°C at 50 rpm. The 5 mL of the sample were withdrawn at 1, 2, 3, 4, 5 up to 6 h. The samples were replaced by an equivalent volume of dissolution medium. The absorbance of the sample was measured by UV-Spectrophotometry at 276 nm.

RESULTS AND DISCUSSION

Formulation F1 & F3 among those hydrophilic matrix tablets formulation we found no delayed drug release in the *in vitro* release study, all those active went in to solution within 2 h. But in the formulation F2 we found satisfactory drug released pattern. We found only 51% drug release after 6 hour of study.

In order to prepare the sustained release tablet, we have observed two things in this experiment

1. Buoyancy property: It has already discussed the importance of bouyoancy property in stomach retention time. And consequently gastric empting rate. Since we found in our experiment that those formulated tablets were floating for almost 8 hours. This approach is practical and cost effective as well as easy to construct.
2. Also we observed the release rate on hourly basis. We had up to six hour long release rate from the matrix tablet. In our experiment we found only formulation-2 gave a satisfactory release rate. Where only 51% levo-salbutamol salphate is were released from that matrix after 6 hours. The other two formulations (formulation 1 & 3) were not that much effective as we see, were completely released after 2 hours. From the above data we can conclude that formulation-2 can be a good candidate in order to prepare sustained release tablet. But still we recommend performing it again for its reproducibility.

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