Development of Dose Sipping Technology, a New Design Approach for Improving Drug Delivery of Acyclovir in Pediatric Medication

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Abstract

Background: In quest of developing a dosage form having increased focus on the development of novel technologies which combines the advantages of liquids as easy swallowing with that of solid dosage forms as storage stability and exact unit dosing as well as taste masking which may improve compliance in children or elderly, dose sipping technology tends to be a better alternative and hence preferred for the present experimental part.

Objectives: The aim and objective of the present work are to study one such new design approach (Dose sipping technology) in order to improve drug delivery of antiviral drugs for pediatric medication.

Method: The proposed dose sipping (DS) administration system consists of Acyclovir drug-loaded pellets formed by the sequential method, further packed in a system of a drinking straw-like tube closed on the bottom end by a filter plug called a controller.

Results: Cumulative drug release data for formulated Acyclovir loaded spheres against marketed Acyclovir tablet using Prototype model forstudyingin-vitro drug release per sip, considering the suction process,achieved 99.70 % release within 11 minutes as compared to 60 minutes for 99.45% with improved patient compliance.

Conclusion: Dose Sipping (DS) Technology is a dosage form which combines the advantages of liquids as easy swallowing with that of solid dosage forms as storage stability and exact unit dosing as well as taste selection in the patient favorite beverage might improve compliance in children or elderly.

Keywords: *Antiviral agent, Dose sipping technology, pediatric medication, new design approach.*

Introduction

Multiparticulate drug delivery systems are composed of a number of discrete units such as granules, pellets or minitablets. Multiparticulate products are expected to provide improved patient acceptability over single-unit solid dosage forms (i.e., tablets and capsules) by dint of their reduced size and thus improved ease of swallowing plus the increased dose flexibility provided by their multi-unit composition.

Multiparticulate can be directly administered into the patients' mouth or dispersed in a vehicle prior to administration as preferred[1,2]. Water, milk, juice or coconut water is potential vehicles commonly proposed. In quest of developing a dosage form having increased

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focus on the development of novel technologies which combines the advantages of liquids as easy swallowing with that of solid dosage forms as storage stability and exact unit dosing as well as taste masking which may improve compliance in children or elderly, dose sipping technology tends[3] to be a better alternative and hence preferred for present experimental part. The aim of the study is to improve the drug delivery by using dose sipping technology for pediatric medication. The objective of this study is study of novel technologies for the preparation of age-appropriate formulations and development of a dosage form which combines the advantages of liquids as easy swallowing with that of solid dosage forms as storage stability and exact unit dosing as well as taste masking which may improve compliance in children or elderly, dose sipping technology tends to be a better alternative and hence preferred for present experimental part. Among various diseases occurring in pediatric patients, HIV infection and their associated opportunistic infections is major cause for mortality and is issue of concern globally. Hence Acyclovir drug used for treating opportunistic infections was preferred for present work.

Experimental Work and Evaluation Data: Present study involves formulation of an Acyclovir drug loaded pellets by sequential method. Following steps were involved: Formulation of Sugar Beads; Formulation of Acyclovir coated beads; Color coat and Filling of straw.

Experimental:

Formulation of Sugar Beads:

Sugar spheres were prepared and evaluated in NM Pharma at Navsal

Formulation of Acyclovir coated beads: The composition of the spray liquid comprises of Acyclovir drug, 0.1 N HCl solution and ethanol. Concentration of 16 % (w/w) was used, which was close to its maximum solubility (18 % w/w in water). Acyclovir was added slowly under continuous stirring to get a uniform dispersion. Drug loading[5] was carried out in R & D coater having speed of around 25 RPM with an optimum temperature of about 60°C. Coating was continued until 22 to 23 % weight gain was achieved. After achieving desired weight gain the coated beads were dried by rotating in pan for 10 minutes. The coated beads thus formed are gently passed through sieve with mesh size 10 and 20**.** Granules retained on 10 # (larger size) and passed through 20 # (smaller size) were discarded. Beads retained on mesh size 20 were even in size and were used to fill in the straws. The Beads were stored in suitable air tight container. Yield was calculated and is recorded.

Color Coat: Prepared Acyclovir coated beads were coated by different colors or flavors like Amaranth, D & C Green-5, D & C Yellow-8, D & C Orange-4 and FD & C Blue-1 by simultaneous method in R & D coater, with temperature 60˚c and 25 RPM.

Filling of Straw: Beads retained on mesh size 20 were even in size and were used to fill in the straws. Twins retained on the sieve were removed. Quantity equivalent to desired dose was accurately weighed and transferred to straw after removal of cap and later closed. The straw was packed in zip lock bag to assure storage stability.

Evaluation:

Evaluation of formulated Sugar Beads: Sugar beads using mentioned tools were evaluated at NM Pharma - **Description** (using lense), **Identification (**using iodine solution), **Particle size (**using sifter analysis method), **Loss on Drying (**using LOD analyser) **Residue on ignition** (using furnace), **Heavy metal (**using AAS), **Assay (on dried basis), Microbial Limit test (**Total aerobic microbial count, Salmonella species determination, Escherichia Coli determinations, Staphylococcus aureus determination and Pseudomonas aeruginosa determination), **Friability and sphericity (**Oscillating Friability Apparatus-Erweka GTA 120). The results are enclosed in table no.1.

Behaviour of sugar spheres in water and different buffer solutions: Sufficient quantity (1g) was placed in beaker containing 10 ml of solutions having pH 7, 6.8 and 1.2 were recorded at different time intervals. The results are enclosed in table no.2.

Table No. 1: Sugar Beads testing parameters and results obtained

Sr.No.	Test	Specifications	Results
1	Description	A white to off-white spherical pellets	A white spherical pellets
2	Identification	A 1:10 suspension give a violet to deep blue colour with iodine TS	A violet colour is produce with iodine TS
3	Specific Rotation	Between + 410 to +610	+52.450
4	Particle size	NLT 90% passes through mesh sieve size (2.36 mm) NMT 10% pass through mesh size (2.00mm)	98.45% 0.60 %
5	Loss on drying (at 1050C for 4 hours)	Not more than 4.0 % w/w	1.28 % w/w
6	Residue on ignition	Not more than 0.25% w/w	0.15 % w/w
7	Heavy metals	Not more than 5 ppm	Complies
8	Assay on (dried basis)	NLT 62.5 and NMT 91.5 %	82.59 %
9	**Microbial Limit test:** (a) Total aerobic microbial count (b) Salmonella species (c) Escherichia Coli (d) Staphylococcus aureus (e) Pseudomonas aeruginosa	 NMT 100 cfu/g Should be absent Should be absent Should be absent Should be absent	 35 cfu/g Absent Absent Absent Absent
10	Friability*	NMT 20 %	0.12 %
11	Spherocity	NLT 0.9	0.98

Table No. 2: Behavior of sugar spheres in water and different buffer solutions:

Sr.No.	pH	Time required to get complete solubalised
1	7.0	1 Min 45 Second
2	8.2	1 Min 42 second
3	1.2	1 Min 15 Second

Evaluation of Acyclovir loaded beads:

- ***In vitro* drug release study of Acyclovir coated beads (Percent drug content determination):** Percent drug content determination was done using UV spectroscopic method. Validated method was developed and applied to Acyclovir coated spheres at 252 nm. Drug content was computed using a calibration curve ($R^2 = 0.9993$).

Drug release study considering suction process:

- **Amount of drug dose sucked per sip:** Dose sipping technology is quite new to regulatory world to get central designed process for studying release pattern[3,4]. Process considering release per suction was also designed and is explained here with. Considering the viscosity parameter and resistance provided by drug coated sugar spheres present in straw, a study was designed. Based upon suction capacity study of group of pediatric volunteers, peristaltic pump was set at around 10-12 RPM. Samples were collected per suction and percent release study was performed using a spectrophotometer at 252 nm. Studies performed revealed that per sip around 6 ml of milk is sucked in 30 seconds i.e 12 ml of milk is sucked per minute and for water 8 ml was sucked in 30seconds i.e 16 ml per minute. Considering this fact we recommend use of milk, water, carbonated drink or coconut water as beverage for fluid to be sucked through drug containing straw.

Comparison with marketed dosage form preparation (Tablet): No product on Dose Sipping is available in market so it was decided to compare the dosage form. Marketed preparation ACIVIR-800 (DT)

was procured from market and drug release study was carried out in triplicate using a USP II tablet dissolution test apparatus (model TDP-06P, Electro Lab, Mumbai, India) at 37±0.5 ºC and 50 rpm. The tablet was place in enzyme-free simulated gastric fluid (900 mL, 0.1N HCl, pH 1.2). A 5 mL aliquot of the dissolution fluid was withdrawn at regular intervals of time and replaced immediately with the same volume of fresh media. The aliquots, following suitable dilution, were analyzed for drug content using a spectrophotometer at 252 nm.

Appearance of drug coating was improved using various colour dyes. Under this 0.5 % weight gain was assisted. Appropriate dosing amount of active coated sugar spheres were filled manually in the straw by removing the cap and leakage from filters after mechanical shaking were evaluated.

Conclusion

During experimentation critical aspect of this technology were observed. It can be concluded that ability to form in-situ suspension with a good mouth feel, attainment of appropriate particle size so that it should not be too small to block the tube (no fine powder), nor too big as to avoid gritty feeling in the mouth (<<1mm). Apart from this neutral taste or in case of bad tasting active ingredients a taste masking for at least the holding time in mouth is important. It can be concluded that in quest of developing a dosage form which combines the advantages of liquids as easy swallowing with that of solid dosage forms as storage stability and exact unit dosing as well as taste masking which may improve compliance in children or elderly, dose sipping technology tends to be a better alternative. Acyclovir one of the important antiviral drug can be successfully delivered using this technology**.** Higher percentage of drug can be easily loaded by this method.

Ethical Clearance: Taken from institutional ethics committee.

Source of Funding: Self.

Conflict of Interest: Nil.

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