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Original Article

DESIGN, FABRICATION AND EVALUATION OF SS 316 PUNCH DIE SET FOR ACCURATE SIZING OF SODIUM CROMOGLYCATE OCULAR INSERTS

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ABSTRACT

Objective: Objective of the study was to design, fabricate & evaluate punch die set for accurate sizing of sodium cromoglycate ocular inserts prepared using few polymers and to compare with physico-chemical results of manually sized inserts.

Methods: The formulated ocular inserts were sized manually and by using punch die set. Ocular inserts sized by manual cutting & stainless steel 316 (SS 316) punch die set was compared and evaluated for various important physico-chemical parameters.

Results: Phenomenal differences were observed in all evaluated parameters like appearance, thickness, drug content and drug release studies. Ocular inserts sized using punch die set had improved appearance, uniform thickness both near the edges & in the center of insert and accurate drug content when compared to ocular inserts that were sized manually. Drug release studies were better for punch die sized inserts as against manually sized inserts.

Conclusion: Ocular inserts sized by punch die set was superior when compared to inserts sized manually. The results for evaluated parameters like appearance, thickness, drug content and drug release studies were accurate, uniform and consistent.

Keywords: Sodium cromoglycate, Punch die set and SS 316.

INTRODUCTION

Eye is a sensitive organ of vision and a challenging subject for topical administration of drugs. A major goal of pharmaco therapeutics is the attainment of an effective drug concentration at the intended site of action for a desired period of time[1]. It was decided to formulate and evaluate sodium cromoglycate extended release ocular inserts for allergic conjunctivitis. Extended release ocular inserts can overcome the limitations of conventional ophthalmic dosage forms thus improving patient compliance with increased therapeutic efficacy [1].

Chemically, sodium cromoglycate is disodium 4,4'-dioxo-5,5'-(-2-hydroxy trimethylenedioxy) di (chromene -2-carboxylate) with a molecular weight of 512.3. Its molecular formula is $C_{23}H_{14}Na_2O_{11}$. The drug is official in major pharmacopoeias like BP, USP and also in Indian Pharmacopoeia (IP) [2].

Three polymers were used to prepare ocular films. A novel natural polymer Pullulan, synthetic polymer namely, Hydroxy ethyl cellulose (HEC) and Gelatin of natural origin were used. Pullulan is a water-soluble neutral polysaccharide produced from starch syrup by fermentation. Available as a white powder, it is essentially odorless, flavorless, and stable [3].

The good binding and film-forming properties of Pullulan make it a valuable ingredient for coating tablet. Pullulan can also be used to make non-animal capsules and has the same exceptional oxygen barrier function as the film [3]. Pullulan is listed on the USP-NF (United States Pharmacopoeia-National Formulary). On the other hand, HEC is partially substituted 2-hydroxyethyl ether of cellulose. It is white, odorless, tasteless, free flowing powder softens at 137°C. Pharmaceutically it is used as a thickener, binder, suspending agent in lotions and ophthalmic solutions [4]. Gelatin is vitreous, brittle solid and is faintly yellow in color. It has got excellent film forming property [4].

Stainless steel 316 (SS 316) was used to fabricate and develop punch die set for accurate sizing of oval shaped ocular inserts having dimension of 8 mm x 5 mm. This In House (IH) SS 316 punch die set was fabricated mainly to avoid variations while manual sizing of oval shaped ocular inserts.

MATERIALS AND METHODS

Materials

(i) Drug and excipients

Sodium cromoglycate was provided by M/s Marck biosciences Ltd, Ahmedabad as a gift sample, Pullulan was procured from TCI Japan, Hydroxyethyl cellulose was received from Color con India as a gift sample, Gelatin was received as a gift sample from SPI Pharma, Bangalore.

(ii) Equipment

Hot air oven (Osworld lab oven), IH fabricated glass mould, IH fabricated SS 316 punch die set, Shimadzu UV Visible spectrophotometer (UV 1601 PC), Mettler Toledo Electronic weighing balance, Calibrated pH meter (EUTECH pH 510), Remi stirrer, Stainless steel scissor and Vernier calipers (Mitutoyo, Japan).

Methods

Standard plot

Sodium cromoglycate is official in Pharmacopoeia's like IP, BP & USP. Indian Pharmacopoeial method was adopted and standard plot of Sodium cromoglycate was carried out using Phosphate buffer saline (PBS) of pH 7.4 [2].

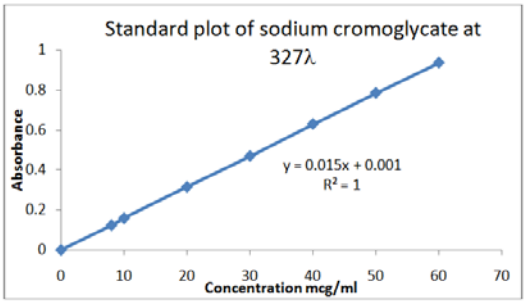

Fig. 1: Standard plot of Sodium Cromoglycate

Preparation, standardization of glass mould & In-House fabricated SS punch die set to cut ocular inserts

In-House fabricated mould made of virgin glass was standardized and used. Each mould was standardized and calculated for number of films that can be prepared for each batch using a particular coded mould. In house designed punch die set was locally fabricated that was made of stainless steel (Grade – SS 316) punch to size uniform oval shaped ocular inserts of dimension 8 mm x 5 mm. Glass mould, punch die set and oval ocular insert is represented below. (The oval shaped insert is shown in fig. 2 on the extreme right side)

Strength per insert

6 mg of Sodium cromoglycate was included in each extended release ocular insert.

Formulation of extended release ocular inserts

Accurately weighed amount of respective polymer was taken and dispersed in known quantity of water for hydration (few minutes) and this was stirred using remi stirrer at 2500 rpm for 25 to 30 minutes for uniform dispersion. Accurately weighed required amount of drug (for each mould) was added to above viscous solution and stirred at 2500 rpm for about 10 minutes. PEG 400 was added as plasticizer and mixed well for uniformity. The resultant mass was poured into a glass mould with and it was dried in tray drier at 50° to 55° C for 4 hours. The dried film was removed carefully and cutting was done both manually as well by using SS 316 punch die set. For manual sizing, punch was used, where the punch impression on ocular insert was used to cut inserts manually by using a sharp stainless steel scissor.

Fig. 2: In-House fabricated glass mould and punch die set and a ocular film of oval shape is shown in extreme right side.

Table 1: Composition of polymers and plasticizers in formulations

Formulation code	Polymer & concentration	Plasticizer*	Drug content in each insert
FC 1	Pullulan 10% w/v	PEG 400	6 mg
FC 2	HEC 10% w/v	PEG 400	6 mg
FC 3	Gelatin 10% w/v	PEG 400	6 mg

*Based on polymer weight

Evaluation of ocular inserts

Ocular inserts sized manually and using SS 316 punch die set was evaluated for various physico-chemical tests like Appearance or description, thickness, drug content and *in vitro* drug release studies by In-House (IH) vial method [5-7]. In-House vial method was used to determine the rate of drug dissolution from the inserts. The dissolution medium used was Phosphate buffer saline (PBS) of pH 7.4. The ocular insert was kept in vial containing 5 mL of PBS of pH 7.4 and samples were withdrawn at different time points.

It was then assayed spectrophotometrically at 327 nm after required dilution with release media. All of the withdrawn samples were replenished with equal volumes of same release medium to keep the release volume constant throughout the experiment.

RESULTS AND DISCUSSIONS

The ocular inserts prepared using three different polymers, Pullulan 10%, HEC 10% and Gelatin 10% were biodegradable in nature. Ocular inserts of both the polymers showed differences with respect to physico-chemical properties such as appearance, thickness, drug content and *in vitro* release studies. The results for ocular inserts sized manually and sized by using punch die set are shown in table 2 and 3 respectively. The in vitro release studies are shown in fig. 3 to 8 respectively.

Table 2: Results for ocular inserts sized manually.

Parameter	10% Pullulan inserts	10% HEC inserts	10% Gelatin inserts
Appearance	Clear to slightly opaque inserts with Slight uneven edges.	Clear to slightly off white in color with uneven edges	Off white to slightly yellow colored films with uneven edges
Thickness# (NMT 0.40 mm)	0.23 Thickness near the edges was more when compared to center of inserts.	0.19 Thickness near the edges was more when compared to center of inserts.	0.30 Thickness near the edges was more when compared to center of inserts.
Drug content@ 5.7 to 6.3 mg [Claim- 6mg/insert]	5.80	5.73	6.23
Drug release studies (IH vial method)	98.5% @ 3 hours	99.1% @ 5 hours	99.6% @ 5 hours

Table 3: Results for ocular inserts sized using SS 316 punch die set

Parameter	10% Pullulan inserts	10% HEC inserts	10% Gelatin inserts
Appearance	Clear to slightly opaque inserts Witheven edges and smooth Finish	Clear to slightly off white in color with even edges and smooth finish	Off white to slightly yellow colored filmswith even edges and smooth finish
Thickness# (NMT 0.40 mm)	0.22 Thickness was uniform near the edges and center of inserts.	0.20 Thickness was uniform near the edges and center of inserts.	0.28 Thickness was uniform near the edges and center of inserts.
Drug content@ 5.7 to 6.3 mg [Claim- 6mg/insert]	6.10	6.0	6.0
Drug release studies (IH vial method)	99.4% @ 3 hours	98.3% @ 6 hours	98.8% @ 5.5 hours

The results for appearance, thickness and drug content of table 2 and table 3 are discussed below in detail.

The Appearance or Description of ocular insert sized manually was not of acceptable quality because of rough and uneven edges, whereas inserts sized by using punch die set was very good in appearance with even edges and fine finish.

One of the important objectives was to maintain Thickness at not more than 0.40 mm. This was complying for inserts that were sized manually as well by using punch die set. However, it was observed that thickness near the edges was more when compared to thickness at center for the inserts that were sized manually. This was not the case with inserts that were sized using punch die set as the inserts were observed to have even thickness across inserts with even & accurate edges and film appearance was at its best.

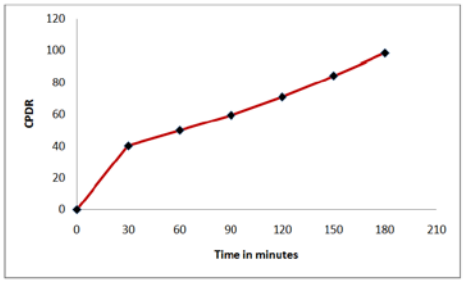

Fig. 3: *In vitro* release studies of sodium cromoglycate from10% Pullulan films (Manually sized)

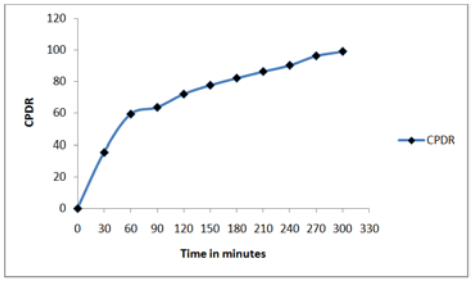

Fig. 4: *In vitro* release studies of sodium cromoglycate from 10% HEC films (Manually sized)

Drug content results were interesting. The input or the label claim for each insert was 6 mg (5.7 to 6.3 mg) i. e, 95% to 105% as per In House specification limit. Drug content of inserts sized by both manual and punch die cutting was passing. But it was noticed that drug content of inserts that were sized manually showed extreme drug content results. For 10% Pullulan inserts and 10% HEC inserts, the drug content was at the lower specification limits at 5.80 mg & 5.73 mg respectively and drug content of 10% gelatin inserts was found to be at higher specification limit at 6.23 mg. But the drug content results were more precise and accurate for the inserts that were sized using SS 316 punch die set. The observed results were 6.10 mg, 6.0 mg and 6.0 mg for 10% Pullulan, 10% HEC and 10% Gelatin inserts respectively.

The following fig. (fig. 3 to 8) depict the *in vitro* drug release profiles of ocular inserts/films sized manually and as well by using punch die set. The plot shows cumulative percent drug release (CPDR) versus time in minutes.

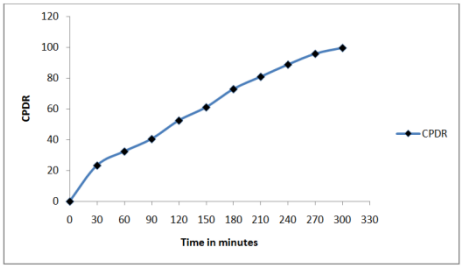

Fig. 5: *In vitro* release studies of sodium cromoglycate from10% Gelatin films (Manually sized)

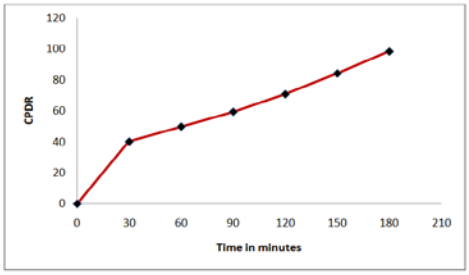

Fig. 6: *In vitro* release studies of sodiumcromoglycate from10%Pullulan films (Punch die cut films)

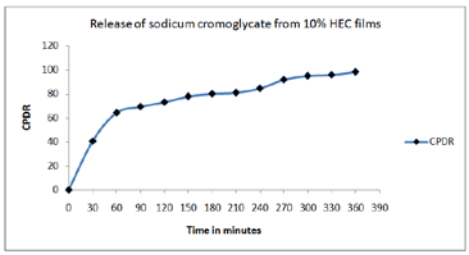

Fig. 7: *In vitro* release studies of sodium cromoglycate from10% HEC films (Punch die cut films)

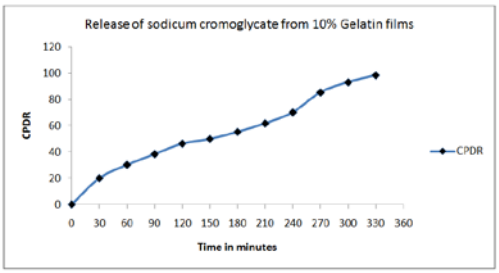

Fig. 8: *In vitro* release studies of sodium cromoglycate from10% Gelatin films (Punch die cut films)

To sum up release studies, the *in vitro* drug release studies for punch die cut inserts/films were much better when compared to inserts that were sized manually. The drug release time was slightly delayed for inserts that were sized by using punch die set as compared to inserts sized manually. This may be due to the fact that, rough uneven edges of manually sized inserts ruptured faster in the dissolution medium.

However there was no differences observed for 10% Pullulan inserts and the drug release lasted approximately for about 3 hours both for manually sized and punch die sized inserts. This may be due to property of Pullulan polymer which resulted in thin soft pliable films / inserts that aided in manual cutting without much difficulty and less damage to edges.

CONCLUSION

From the results, it is very much evident that phenomenal differences are observed with respect to physico-chemical results of ocular inserts that were sized manually as well by using SS 316 punch die set. Appearance and thickness was it at best for inserts that were sized by using SS 316 punch die set. Drug content results were major concern for inserts that were sized manually, as the results were either at lower or upper limits with respect to specification.

Drug release was delayed for inserts sized by punch die set when compared to manually sized inserts. Finally, it is concluded that SS 316 punch die set shall result in an ocular insert that will comply all the physico-chemical parameters as per specification limits and also result in batch to batch consistency and reproducibility.

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CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Chien YW. editor. Novel Drug Delivery Systems. 1st ed. New York: Marcel Dekker Inc; 1982.
2. Sodium cromoglycate–Monograph, Indian Pharmacopoeia. 5th ed. Vol 3, Ghaziabad: Ministry of Health and Family Welfare, Government of India; 2007. p. 1715-7.
3. http://www.Intl.hayashibara.co.jp/products.php?jpml=products_pharmaceuticals_pullulan. [Accessed on 15/06/2013].
4. Handbook of Pharmaceutical Excipients. Vol. I. USA: American Pharmaceutical Association and the Pharmaceutical Association of Great Britain; 1986. p. 119-31.
5. Aburahma MH, Mahmoud AA. Biodegradable ocular inserts for sustained delivery of brimonidine tartarate: preparation and *In Vitro/In Vivo* Evaluation. AAPS Pharm Sci Tech 2011;12(4):1335-47.
6. Nautiyal D, Singh V, Ali S. Formulation and evaluation of sustained release of ofloxacin ocular inserts. Res J Pharm Tech 2012;5(12):1497-9.
7. Pai KG, Reddy MS. Formulation and evaluation of extended release ocular inserts prepared from synthetic & natural biodegradable–biocompatible polymers. Res J Pharm Tech 2014;7(1):48-51.