Controlled Release of an OTC Cough Suppressant in a Soft Gelatin Based Dosage Form

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PURPOSE

The purpose of the present study was to design a controlled release soft gel capsule based drug delivery system for a model cough suppressant drug. Soft gel capsule is a very commonly available dosage form for various medications as it offers several advantages like delivering liquid and lipid (oil) based medications, taste masking, aesthetic appearance and many more. However, manufacturing of soft gel capsules is often limited by high viscosity of liquid fill and higher temperatures needed to encapsulate these viscous fills. Purpose of this study was to show a formulation approach leading to selection of a fill material which is amenable to easy encapsulation process while retaining desired controlled release characteristics from capsules.

OBJECTIVE(S)

Objective of this study was to screen various hydrophobic and hydrophilic waxes and polymers with controlled release technology (Versatrol) to formulate a model cough suppressant drug. Two approaches were explored using a proprietary controlled release technology (Versatrol): hydrophilic carrier-polymer based matrix and lipophilic carrier-high melting wax matrix. Several polymers and waxes were also explored in combination to achieve extended release of the drug and easy encapsulation process.

METHOD(S)

Solubility study:

Preliminary solubility studies for the model drug were conducted in various pharmaceutical excipients (lipid vehicles) to choose appropriate bulk liquid carriers for both approaches. Known amount of drug was added to vehicle and heated until 45-50˚C to melt the excipients. Vehicle were checked for solubility based on clarity of the solution and solutions were left to stand 24 hour to check any precipitation.

Preparation of fill formulations:

Polymers and/or wax were mixed with a suitable vehicle to form binary/tertiary mixtures. These mixtures were heated or homogenized to obtain a homogenous mixture in hot air oven or homogenizer, respectively. The mixtures were homogenized when heating was not needed (e.g. in case of polymeric excipients in vehicle) while the mixtures were heated when heat was necessary to obtain homogeneous mixture (e.g. melting of wax with lipid vehicle). After obtaining homogeneous mixtures, they were cooled to room temperature before adding the API in the mixture. After adding the API, the mixtures were homogenized using handheld homogenizer.

Evaluation of capsule fill formulations

Formulations were characterized for sedimentation rate, flowability and viscosity. Fills manufactured with two different approaches were also evaluated for the impact of hold time on physical properties and encapsulation. For preliminary evaluations, fill was dispensed into two-piece capsules for dissolution performance evaluation. The lead candidates from both approaches were encapsulated into soft gelatin capsules and evaluated for dissolution in simulated gastric fluid (SGF) at pH 1.2. Apparatus II method at 50-100 rpm was employed for the dissolution experiments.

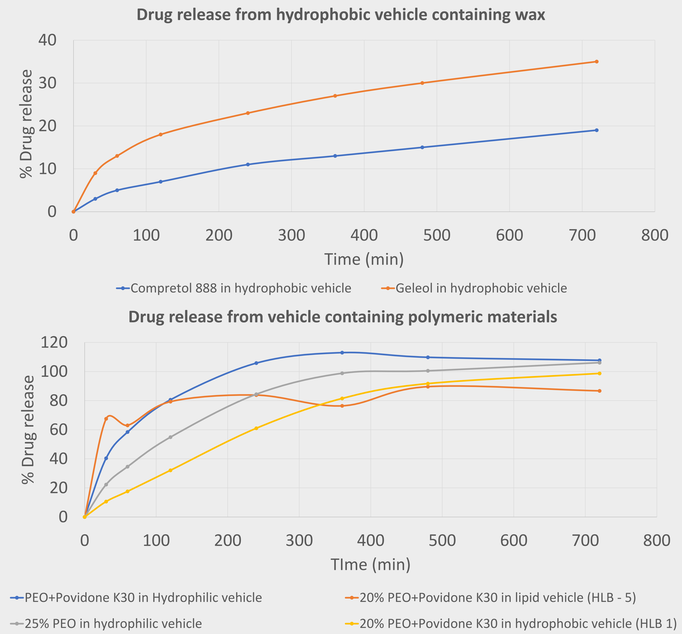
Stability study

Capsules of the selected formulations were bottled into HDPE bottles with the use of child resistant closures and induction sealed for ICH stability studies.

RESULT(S)

Fill formulations based on hydrophilic and hydrophobic vehicles mixed with wax/polymers and their characterization for encapsulation and drug release.

Evaluation of formulation	Oil based vehicle		Hydrophilic vehicle	
	Compritol 888 based fill	Gel oil based formulation	PEO based fill	PEO/Povidone Based fill
Melt temperature/ Homogenization	Clear liquid above 70˚C	Clear liquid at temp >60˚C	Flowable. Homogenized at 50˚C	Flowable. Homogenized at 50˚C
Fill flowability below 40˚C	Solidifies below 50˚C	Flowable at 40˚C	Flowable at room temperature	Flowable at room temperature
Drug release	Incomplete drug release due to insoluble lipids	Incomplete drug release due to insoluble lipids	Complete drug release. Variable release with different PEO concentrations	Complete drug release. Variable release with different PE/Povidone concentrations
Encapsulation	Difficult/Not feasible	Feasible at 40˚C	Feasible at room temperature - Fill became viscous after 24 hours	Feasible at room temperature - Fill became viscous after 24 hours-difficult encapsulation



Percent drug release (%) vs time (min) graphs for different fill formulat6ions based on hydrophilic and hydrophobic vehicles. The graph on top shows drug release from hydrophobic matrix while graph on bottom shows drug release from hydrophilic vehicle mixed with polymeric materials. Data shows average of two determinations (n=2).

RESULT(S)

- From a softgel encapsulation standpoint encapsulation process works with maximum fill temperature of 42 °C. Above this temperature encapsulation process could face potential capsule sealing and leaking issues.
- For compritol 888 and other wax based hydrophobic fill approach, encapsulation was only feasible at a temperature range of 37-42 °C while hydrophilic vehicle based fills could be encapsulated at room temperature. However, hydrophilic vehicle based fills became very viscous after 24 hr storage as a result of PEO and Povidone K30 hydration.
- Dissolution in simulated gastric fluid (SGF) showed controlled release of the drug up to 12 hour from both approaches. Polyethylene Oxide (PEO) and Povidone K 30 were used with the hydrophilic vehicles as well as hydrophobic vehicles. Use of hydrophilic vehicles (HLB > 14) which had solubilizing capacity for the drug, resulted in an initial burst effect as seen from blue line in graph 2. (PEO + Povidone K 30 in hydrophilic vehicle). When the high HLB (hydrophilic-lipophilic balance) vehicle was switched with excipients in an HLB range of 9-12, the burst effect was mitigated. Faster rate of drug sedimentation was noted for the hydrophilic Povidone/PEO based systems as compared to the lipidic systems.
- High variability for drug release was noted for wax/hydrophobic vehicles as compared to polymer/hydrophilic vehicles. In both instances, a diffusion-based release mechanism was noted. However due to very low solubility of wax in the dissolution media only 30-40% of the drug was released from capsule.
- With the use of lipophilic based systems, the burst effect was eliminated which can be attributed to limited API solubility in the lipophilic vehicles and the use of high melting lipid (HML) excipients such as Compritol 888 (glyceryl dibehenate), Precirol (glyceryl distearate). However the release from these matrix were variable and incomplete as shown in graphs.

CONCLUSION(S)

- For antitussive agents with a short half-life, the approaches discussed in this work can yield sustained release dosage forms to avoid repeated administrations and increase patient compliance. Moreover, composition of the formulation can be tuned to make it feasible for encapsulation while retaining the controlled release efficiency of the formulation.
- The controlled release formulations presented in this research could potentially be deployed for OTC and prescription molecules across a wide range of therapeutic areas. In addition, the hydrophilic vehicle-based formulations which displayed the burst effect could be explored for combination drugs that need immediate and controlled release delivery.

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