Sudarshan Publication

Available online at S-epub.in/ojs/

THE PHARMA RESEARCH
An International Journal of Pharmacy Research

FORMULATON AND EVALUATION OF MEDICATED SOLUBLE CHEWING GUM CONTAINING FEROSEMIDE

Mittal Anuj[1]*, Kumar Ajay[2], Anup Maiti[3]

1. Prasad Institute of Technology, Jaunpur, India
2. Government Pharmacy Institute, agamkua, Patna, India
3. RRS college of Pharmacy, Amethi, India

ARTICLE INFO

Published on: 15-03-2017
ISSN: 0975-8216

Keywords:
Ferosemide, Chewing, Gum, Medicated

Corresponding Author:
Anuj Mittal, Prasad Institute Of Technology, Jaunpur, India

ABSTRACT

An attempt has been made to formulate new medicated soluble chewing gum for ferosemide. The new drug delivery system was obtained, at room temperature, by hot melt extrusion method. The resulting chewing gum comprises a gum core combined with fillers, coloring agent and plasticizers, which provide smooth appearance and flexibility during storage and chewing. Drug release from a dosage form is the critical step in drug absorption and bioavailability, thus an experimental work has been designed to evaluate the efficiency of this kind of therapeutic system by verifying its capability to release the drug dose and by assessing the delivery of ferosemide for by-passing the hepatic first pass effect. Simple diffusion into the medium causes the release of only a small percentage of the drug contained in the medicated chewing gum, while the delivery of the major part of the dose occurs during mastication. Different formulations of chewing gum with varying concentration of plasticizers like glycerol and castor oil were formulated. Better consistency of formulation and faster release of drug in saliva was obtained with glycerol A1 .Buccal absorption test showed that 90.4% of drug absorbed within 5.4 min when available to the buccal mucosa at pH 5.5 and simulated salivary fluid release was 89.78%. Hence, ferosemide chewing gum can be considered as a better formulation for the buccal drug delivery system, in which drug is absorbed buccally and reaches the systemic circulation via jugular vein.

INTRODUCTION

Despite phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route. There are of course many applications and large markets for non-Oral products and the technologies that deliver them.[1]

The oral route of administration is the most popular and successful route used for conventional drug delivery because of convenience, ease of administration, greater flexibility in dosage form design, ease of production low cost of such a system and hence adopted wherever possible.[2]

It is well known fact that the right drug delivery system is critical to the success of a pharmaceutical product. Pharmacological active agents or drugs are formulated into variety of dosage forms like It is well known fact that the right drug delivery system is critical to the success of a pharmaceutical product. Pharmacological active agents or drugs are formulated into variety of dosage forms like tablets, capsules, injectables, inhalers, ointments etc considering physicochemical properties, pharmacokinetic & pharmacodynamic parameters and biopharmaceutical aspects of drugs. In addition to its confectionary role, Chewing Gum (CG) also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients.

A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and thus increase revenue.tablets, capsules, injectables, inhalers, ointments etc considering physicochemical properties, pharmacokinetic & pharmacodynamic parameters and biopharmaceutical aspects of drugs.

Chewing Gum (CG) also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients. A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and thus increase revenue.[3]

The first commercial chewing gum "State of Maine pure spruce gum" was marketed in 1948 in the U.S.A. The first patent was filed in 1869. The gum was intended as dentifrices but could not be marketed. The first Medicated chewing gum "Aspergum" was launched in 1928. This chewing gum is still available and contains acetylsalicylic acid.[4]

In the present work, ferosemide drug is used, which is a benzoic-sulfonamide-furan. Furosemide is a loop diuretic (water pill) that prevents your body from absorbing too much salt, allowing the salt to instead be passed in your urine. Furosemide treats fluid retention (edema) in people with congestive heart failure, liver disease, or a kidney disorder such as nephrotic syndrome. This medication is also used to treat high blood pressure (hypertension). Ferosemide is 60% absorbed in patients with normal renal function 95% bound to plasma proteins. The elimination half-life is 2 hours. The approach of this study was to design a chewing gum where the complete release of the drug dose from the formulation can be detected from the organoleptic change of the gum independently of the different chewing times and chewing frequency of the patients. Here ,synthetic polymer is used as a base for chewing gum with different plasticizer, sweetener, colorants, fillers etc.for that we have to study some evalution parameters like ,release of drug in saliva.[5]

MERITS OF MCG[6]:

- It does not require water to swallow. Hence can be taken anywhere.
- It is advantageous for patients having difficulty in swallowing.
- It is excellent for acute medication.

- It counteracts dry mouth, prevents candidiasis and caries.
- They are highly acceptable by children.
- It provides pleasant taste.
- It avoids first Pass metabolism and thus increases the bioavailability of drugs.
- They show fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
- Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
- Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa.
- Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.[6]

COMPONENTS OF MCG[7]:-

1. **Elastomers**: They provide elasticity and cohesion to the chewing gum. Natural elastomer,natural rubbers like latex or natural gums such as Jelutong, Lechi Caspi, Perillo, Chicle and synthetic elastomers like polyisobutylene, polyvinyl pyrrolidone and butyl rubber are used.
2. **Plastisizers**: These are used to regulate cohesiveness of product. These are again divided into Natural and Synthetic. Natural Plastisizers include Natural rosin esters like Glycerol esters.
3. **Fillers or Texturizers**: Provide texture, improve chewability, provide reasonable size of the gum lump with low dose drug. Commonly used fillers are Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminium Silicate, Clay, Alumina, Talc etc.
4. **Softners and Emulsifiers:** These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. Softners include Glycerin, Lecithin etc.
5. **Colourants and Whiteners** may include FD & C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.
6. **Sweetners:** These are of two types, Aqueous and Bulk. Aqueous Sweetners can be used as softners to blend the ingredients and retain moisture. These include Sorbitol, hydrogenated Starch hydrolysates and Corn Syrups.
7. **Flavouring Agents:** A variety of flavouring agents are used to improve flavor in chewing gum includes essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil and Oil of Wintergreen

MATERIALS AND METHOD:

MATERIALS: Ferosemide was a gift sample.Polyvinyl pyrrolidone used as asynthetic elastomer.glycerol,castor oil were used as a plasticizer with a varying concentration. Sucrose and sorbitol as sweetener, peppermint as a flavouring agent and talc was used as filler.

MANUFACTURING PROCESS:

FIRST METHOD[8]-

Conventional/Traditional Method: Components of gumbase are softened or melted and placed in a kettle mixer to which sweeteners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that form into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. In a carefully controlled room, the gum is cooled for upto 48 hours. This allows the gum to set properly. Finally the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.

SECOND METHOD[9]-

Step 1: The gum base ingredients are melted together and filtered.

Step 2: Powdered sugar, glucose syrup, flavoring and the other ingredients are slowly added to the gum base until the warm mixture thickens like dough.

Step 3: Machines called extruders are used to blend, smooth and form the gum.

Step 4: It's time for the gum to be shaped. Gum can be flattened ,cut into sticks or squeezed into a rope shape bladed into chunks or molded into different shapes and finally candy coated.

Step 5: After the gum is cut or molded into the appropriate shape, it is lightly sprinkled with powdered sweetener to keep it away from sticking to machinery or packaging.

Step 6: In a carefully temperature controlled room, the gum is cooled for up to 48 hours. This allows the gum to properly set.

Step 7: If the gum is candy coated like most gum balls or pellet gum, it is sprayed with liquid sweetener, allowed to dry and then sprayed again. This process is repeated several times until the candy shell reaches the proper thickness.

Step 8: High speed machines carefully wrap and package the gum in air tight wrappers. This ensures the gum fresh and soft upon opening of the pack.

THIRD METHOD[10]:-

1. The making of gum begins by preparing gum base. If gum base is natural, it must first be harvested and processed. The process begins by melting and purifying the gum base. Which is placed in a warm room to dry for a day or two (hot air continually passed over the mixture).It is then sterilized and melted in a steam cooker.
2. The substance is then pumped to a high-powered centrifuge to rid the gum base of undesirable dirt and bark.
3. The cooked base is mixed with softeners, sweeteners and all others additives.
4. The next step is kneading. Extruders (machines) are used to blend, smooth and form the gum mass.
5. A cutting machine cut the sheets into sticks or small pellets which are later on candy coated.
6. Other machines then carefully wrap and package the gum in air tight wrappers.

FOURTH METHOD[11]:- Hot melt extrusion-The method comprises of mixing of elastomer, plasticizer and the drug filler ingredients by suitable blending mechanism. The hot melted liquid containing sweetner, softner and flavouring agents was added to the blended mass. The mixing was continued and finally moulded in appropriate shapes. At the end, moulded bodies were cooled and powder coated to enhance their aesthetic properties.

TABLE 1: Formula of ferosemide soluble chewing gum with different concentrations of plasticizer.

Ingredients	A1	A2	A3	A4	A5	A6
Glycerol	16	20	24	-	-	-
Castor oil	-	-	-	16	20	24
PVP	300	200	100	300	200	100
Ferosemide	200mg	200mg	200mg	200mg	200mg	200mg
Paraffine wax	100	200	300	100	200	300
Cal.carbonate	150	150	150	150	150	150
Peppermint	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Sucrose	350	350	350	350	350	350
Sorbitol	5ml	5ml	5ml	5ml	5ml	5ml

EVALUATION PARAMETERS:

Physical Characterstics:

The properties of synthetic gum base and formulations were reported on the basis of their color, sweetness, chewability, solubility, flavours, stikiness and hardness.

Table-2 Results of physical parameters.

Sr.no	Parameters	A1	A2	A3	A4	A5	A6
1.	**Appearance**	Soft solid	Soft solid	Soft solid	Soft solid	Soft solid	Soft solid
2.	**Colour**	White	White	White	Off white	Off White	Off White
3.	**Hardness**	5	5	5	5	5	5
4.	**Stickiness**	least sticky	Sticky	Sticky	Sticks after chewing	Very sticky	Sticky
5.	**Sweetness**	Excellent	Good	Good	Good	Good	Excellent
6.	**Flavours**	Excellent	Good	Good	Excellent	Good	Good
7.	**Solubility**	Quickly soluble	soluble	Good	Good	Quickly soluble	Good
8.	**Chewability**	Excellent	Soft	Soft	Chewable	Good	Good
9.	**Flexibility**	7.3cm	5.4cm	4.6cm	6.6cm	4.1cm	5.3cm
10.	**Texture**	Very Good	Good	Fair	Good	Very good	Good

EX- VIVO 'CHEW-OUT' STUDIES:

Release of drug in saliva:

With given instructions volunteers were instructed to rinse their mouth with distilled water and allowed to chew the medicated chewing gum for maximum 8 minutes. They were also instructed not to swallow the chewing gum and saliva, after complete solubilization they were said to rinse their mouth with 10ml of water which was collected & diluted to 50ml with 50% methanol and filtered with 0.02 micron nylon filter so that its maximum release had to be taken and absorbance was determined spectrophotometrically.

In-vitro release study in 'simulated salivary fluid':

SIMULATED GASTRIC FLUID[12]:

Preparation of Simulated Salivary Fluid: To prepare simulated salivary fluid, a 5 % mucin solution was first prepared by adding 200 ml of deionized water to 10 g of mucin and stirring the mixture until dissolved completely. Then following ingredients were mixed, in the order listed below, in about 800 ml of deionized water with slow stirring:

Table No3 Composition of simulated gastric fluid

Sl. No.	Ingredients	Quantity in1000 ml
1.	$NaNO_2$	0.01gm
2.	$MgCl_2$	0.03gm
3.	$CaCl_2.2H_2O$	0.21gm
4.	NaCl	0.61gm
5.	KH_2PO_4	1.63gm
6.	K_2HPO_4	0.50gm
7.	KCl	1.0gm
8.	$NaHCO_3$	0.25gm
9.	THIMEROSOL	0.20gm
10.	AMYLASE	0.725gm
11.	MUCIN (5%)	2.0ml
12.	ANTIPAIN 50µG/ML	0.05gm

It was analysed by adding the sample of produced chewing gum in beaker of dissolution apparatus containing 200ml of simulated salivary fluid so as to solublize completely.The absorbance was recorded after the 5, 10, 15, 20, 25 min time intervals. Accordingly concentration of released amount of drug was determined with respect to the different samples withdrawn at given period of time.

IN-VITRO DISSOLUTION

The comparative study of formulations A_1-A_6 showed that A_1 gave the best result as compared to others and hence formulation A_1 was considered as best batch of soluble medicated chewing gum.

In-vitro dissolution profile of formulation A_1 _A_6in simulated salivary fluid:

Table-4 Comparative Release kinetic data of formulation A_1 - A_6 in simulated salivary fluid.

Srno	Time (mins)	% Release					
		A_1	A_2	e A_3	A_4	A_5	A_6
1.	5	28.27	25.66	25.19	26.22	24.16	24.22
2.	10	45.39	42.66	42.32	43.38	43.15	46.62
3.	15	63.42	57.93	64.11	65.21	61.12	60.89
4.	20	80.24	74.75	74.05	76.34	72.23	68.32
5.	30	**89.78**	76.87	80.54	81.12	79.83	75.11

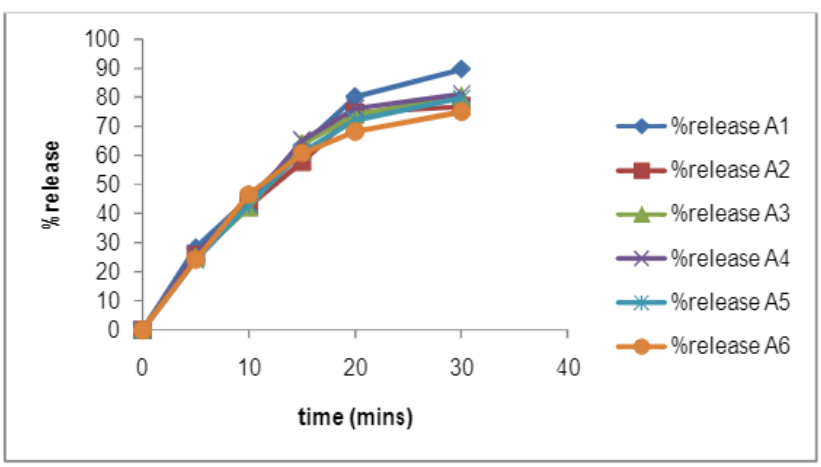

Figure-1 Comparative release profile of batches A_1–A_6

Ex vivo studies

Ex-vivo salivary release of formulation A_1_ A_6

Table-5 Percent drug release v/s time data of A_1_A_6 blend.

Formulations(A1-A6)	Time(mins)	% Release
A_1	5.4	90.4
A_2	7.5	80.6
A_3	6.5	83.3
A_4	6.0	75.5
A_5	5.0	79.6
A_6	6.0	80.4

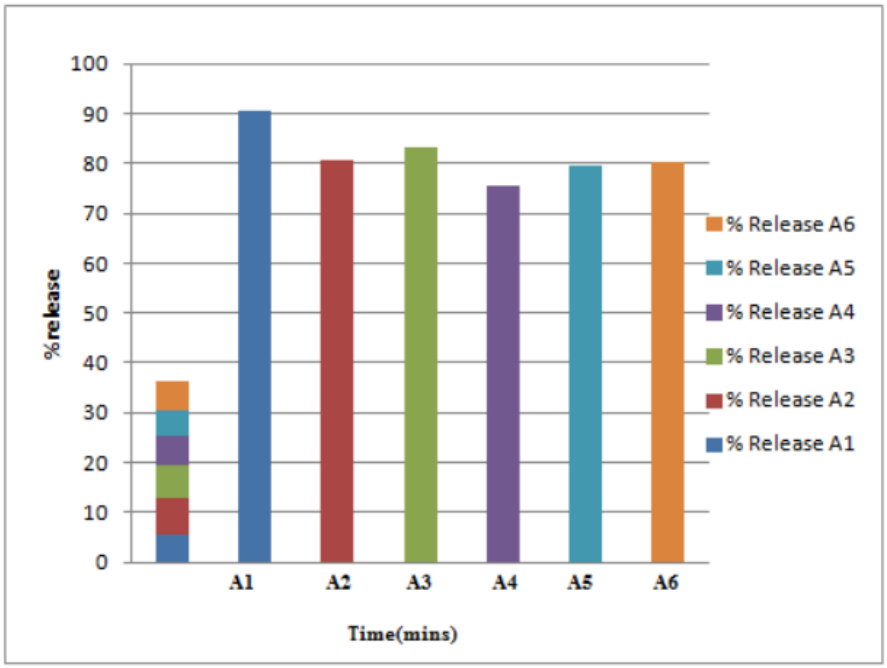

Figure-2 Comparative salivary release profile of batches A_1- A_6

Evidently percentage release profile of A_1 formulation showed the optimum (90.4%) and was selected for stability studies.

STABILITY STUDY OF OPTIMIZED FORMULATION A_1:

The stability studies were performed on prepared formulations as per ICH guidelines at 45 ± 2^0C and 75%±5% relative humidity which showed that the formulation suffered no physical changes

Table-6 Physiochemical properties of medicated chewing gum after 30 days accelated stability studies

Sr.no	Physiochemical properties	A_1
1.	Colour	No change
2.	Softness	No change
3.	Texture	No change
4.	weight	Remained same
5.	Taste	No change

CONCLUSION:

From the above studies, it was concluded that polyvinyl pyrrolidone is a synthetic gum base used in chewing gum preparations. It shows better compatibility and it is easily available and cheap. After the chewing of ferosemide chewing gum formulation for 5.4 min., some drug was buccally absorbed. Some amount was analyzed from expelled saliva and remained amount was in the formulation, in the residual form. Hence, ferosemide

chewing gum with glycerol can be considered as a better formulation for buccal drug delivery system in which drug is absorbed buccally and reaches circulation via jugular vein. Only a small portion of drug is carried with saliva in gastrointestinal tract that is in dissolved and dispersed form, hence can be absorbed easily. Finally, chewing gum as a buccal drug delivery can be considered as faster and novel drug delivery system for drug to avoid first pass effect, reduce risk of over dosing, easy administration and faster action.

REFERENCES

1. **Furness Guy**; *"Oral Drug Delivery"***Ondrugdelivery.,2007;pp-3-25.**
2. **C.K Sompur; Doijad.C.R; Patil.M.S; Maske P.A**, *"An Approch For Development Of Oral Sustained Release Suspension"***Ijpbs.; 2011;Vol.2 (2);pp-320-329.**
3. **K.Ezhumalai**, *"Medicated Chewing Gum-A Novel Drug Delivery Technique For Systemic And Targeted Drug Delivery"* **Ijpt, March-2011;Vol. 3(1) 725-744.**
4. **B Shrinivas Bumrela; N Rajesh Kane**, " *Medicated Chewing Gum: New Reformulation Technique"*,**Pharmainfo.Net,Vol3(4),2005**
5. **http://www.drugbank.ca/drugs/DB00695**
6. **Pratik Savaliya; Mahesh Kalathiya**, *"Chewing Gum A Modern Era Of Drug Delivery"*, **Irjp; 2011;vol 2(10),7-12**
7. **Jain Hitesh; Shah Mansi; Pasha.T.Y**, *"Medicated Chewing Gum: A Novel Oral Drug Delivery"*,**International Journal Of Drug Formulation & Research;2010;Vol. 1(iii);80- 96**
8. **Gadhavi A.G;Patel B.N;Patel D.M**, "*Medicated chewing gum - a 21st century drug delivery system"* , **IJPSR, 2011; Vol. 2(8): 1961-1974**
9. **Http://Www.Gumassociation.Org/Default.Aspx?Cat=2**
10. **Http://Www.Chewinggumfacts.Com/Making-Chewing-Gum/How-Chewing-Gum-Is-Made/**
11. **NagaichUpendra; Chaudhary Vandana; Yadav Akash,** *"Formulation Of Medicated Chewing Gum Of Ondansetron Hydrochloride And Its Pharmacokinetic Evaluations"*, **Ijpsr; (2010); Vol. 1 (2).**
12. **Goldstein A. S**; *"Synthetic oral fluid standard"*, **United States Patent**, 1996; Patent no. 5,736,322.