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Research Article

DISSOLUTION ENHANCEMENT OF A POORLY SOLUBLE MODEL DRUGS USING DIFFERENT FORMULATION APPROACHES FOR IMMEDIATE RELEASE SOLID DOSAGE FORM

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ABSTRACT

The purpose of this study was to endeavor Bilayered tablets (SNFML) and to enhance the in vitro release rates. Several techniques were comparing for improving the dissolution of model drugs SNFML (poorly soluble drugs). Particle size reduction was done by jet milling (Micronization of SNML), use of solubility enhancers like Klucel-Lf and sodium lauryl sulphate, reduction of surface energy by co-sifting and SNML with lactose showed the immediate release profile when compared with the unmicronized drug. Micronization of SNML improved its dissolution rate in Discriminative media (8.2% in 30 min) compared to unmicronized drug (1.3% in 30 min). SNML drug products commercially available on the global markets dissolved similarly to unmicronized SNML, but significantly slower than the micronized drug. The results recommend that Micronization, use of solubility enhancers and reduction of surface energy by co-sifting are powerful traditions for the preparation of immediate release formulations of SNFML, and could potentially show the way to improvements in the bioavailability of oral SNFML products.

Keywords: Poorly water-soluble drugs; Dissolution enhancement; Hydrophilic polymers, Micronization; SNFML.

INTRODUCTION

SNFML is commonly used in the treatment of allergic rhinitis is an inflammation of the nasal passages, usually associated with watery nasal discharge and itching of the nose and eyes.

Fixed-dose combination drug products may improve medication compliance by reducing the pill burden of patients, as well as any usual advantages of combination therapy.

Dissolution of drugs from solid dosage forms is a key parameter in assessing the product quality and uniformity at the formulation stage and as well as throughout the shelf-life of the product. The significance of a dissolution test is based on the fact that for a drug to be absorbed and available to the systemic circulation, it should be in solution form. For Poorly water-soluble drugs, difficulties are usually encountered in selecting a dissolution medium of acceptable volume and composition as well as a good discriminating power.

Many techniques like (1) Size reduction is used to produce small particle size of active ingredients to assure a maximum surface area for solubilization and bioavailability. (2) The possibilities to modify the saturation solubility of drug are to change the dissolution media, usually by changing of the pH, adding of surfactants or using of non-aqueous solvents and (3) Co-sifting can apply for per oral solid preparations of various poorly water-soluble drugs which can reduced the surface energy so that to enhance the dissolution of the tablet formulation which possess problems in the bioavailability.

Materials and methods

Materials

Microcrystalline Cellulose (FMC biopolymer-U.S), Lactose Monohydrate (Signet Chemical-U.S), Hydroxy Propyl Cellulose (Signet Chemical-U.S), Croscarmellose sodium (FMC biopolymer-U.S), Magnesium Stearate (Sigma-Aldrich-U.S), Ferric oxide yellow (Signet Chemical-U.S), Starch 1500 (Roquette-France), Opadry (Colorcon-India), Aerosil (Evonik-Germany). SNML (drug) and SNF (drug) are taken from Sanofi-Synthelabo, Goa-India.

Solubility of the model drugs in various media / solvent

The solubility of SNF and SNML were determined in various media / solvent by shake flask method.

Pre weighed drug was added individually into the test tube and shake until it not saturated. Now calculate the remaining weighed quantity of the drug which is remaining after adding to the various pH media.

Table1: Solubility of the model drugs in various media / solvent

Media	Solubility in mg/ml				
	SNF(drug)	SNML (drug)	SNML+ 0% sls	SNML +0.2% sls	SNML + 0.5%sls
P.w	2.16	0.01	0.13	0.15	**0.56**
pH 1.2	0.2	0.01	0.01	0.08	0.09
pH 3.0	**2.59**	0.01	0.01	0.09	0.24
pH 4.5	0.31	0.01	0.01	0.08	0.42
pH 6.8	0.17	0.01	0.01	0.08	0.07
pH 6.9	0.19	0.01	0.01	0.09	0.45

Bi-layer tablet formulations

The present study was undertaken to formulate a combination of SNF and SNML immediate release bilayered tablets. The study involved preformulation of drug and excipients, formulation and processing development alone with evaluation of the tablets made with optimized formulation. After formulation the limitation for improving dissolution according to certain special release profile products like Immediate Release ≥85% in 30 minutes. This can be achieved by the several formulation methods like Micronization of the drug, uses of solubility enhancers, reduction of surface energy by co-shifting.

Table2: Different trials for making bi-layer tablet formulation with different technique

Formulations	Different concentration of drugs-excipients used for formulation						
	SNF (%)	SNML (%)	Pharmatose (%)	Avicel (%)	Ac-di-sol (%)	Sicovit-yellow (%)	Mg stearate (%)
SNFML-1	30	-	-	33	36	0.5	0.5
SNFML-2	30	-	-	34	35	0.5	0.5
SNFML-3	30	5.2	45	37	11	0.8	1

SNFML-4	30	5.2	44	36	13	0.8	1
SNFML-5	30	5.2	45	36	12	0.8	1
SNFML-6	30	5.2	44	37	12	0.8	1
SNFML-7	30	5.2	44	36	12	0.8	1
SNFML-8	30	5.2	86.3	8	-	0.25	0.25

Determination of bulk density, tapped density and Compressibility index

Bulk density was calculated in g/ml using the formula $\mathbf{M/V_o}$ ……1

Tapped density was calculated in g/ml by the formula $\mathbf{M/V_f}$ ……2

Compressibility index, calculated by the formula

$$C.I = 100 \frac{(Vo - Vf)}{Vo} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 3$$

Loss on Drying

Determinations of loss on drying of granules are important. Drying during granulation was optimized depending upon the LOD value. LOD of different batches were tasted at 60ºC and 105ºC by using Sartorius electronic LOD measurement device.

Sieve analysis

Particle size analysis of granules was measured by using Retsch AS 200 Sieve Shaker. The entire sieve was weighed in descending order. Previously weighed granules were put in sieve shaker. Start the sieve shaker for 5 min at 0.5 mm/g amplitude. Again the entire sieve was weighed in previous manner and calculated the cumulative percentage retained.

Tablet size

Thickness of the tablet was measured by 'Mitutoyo' thickness tester in mm.

Hardness test

Hardness test was carried out by using 'Scheleuniger' hardness tester.

Friability test

Friability of the tablets was tested using a friabilator (friability test apparatus, Electrolab, Mumbai.). A loss of less than 1% in weight was accepted.

The weight of 10 tablets was noted initially (W_1) and placed in the friabilator at 4 min/ 100rpm.The tablets were reweighed and noted as (W_2). The difference in weight is noted and expressed in percentage.

$$\text{Percentage Friability} = \frac{(W_1 - W_2)\ 100}{W_1} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 4$$

Weight variation test

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in the table none deviates by more than twice the percentage.

Evaluation for In-vitro dissolution in different media

Tablet dissolution was assessed using standard USP 24 apparatus II in 900 ml of different buffer medium (pH 0.001 N HCL, 4.5 Acetate buffer, 6.8 phosphate buffer) the stirring speed was 50 and 100 rpm. Total 6 tablets were taken for test. Temperature was maintained 37± 0.5ºC throughout the experiment. Dissolution study was carried out for 1 hr. sampling intervals were 10 min, 15 min, 30min, 45 min, and 60 min. After collection of sample in each interval, dissolution medium was replenished with the same volume of respective medium. Samples were withdrawn at regular intervals and diluted to 100 ml with corresponding medium and analyzed for drug content spectrophotometrically.

RESULTS

Physical properties of granules

Bulk density, Tapped density, compressibility index, Hausner ratio and sieve analysis were presented below.

Table3: Physical properties of granules

Formulations	% Loss on Drying	Bulk density(g/ml)	Tapped density(g/ml)	% compressibility index	Hausner ratio
SNFML-1	1.21	0.404	0.517	22.00	1.282
SNFML-2	1.17	0.478	0.543	12.00	1.136
SNFML-3	1.20	0.509	0.638	20.21	1.254
SNFML-4	1.35	0.470	0.521	14.00	1.145
SNFML-5	1.37	0.512	0.640	20.00	1.250
SNFML-6	1.12	0.502	0.596	19.00	1.198
SNFML-7	1.23	0.493	0.582	18.50	1.192
SNFML-8	1.15	0.530	0.650	19.10	1.200

Sieve analysis

Particle size analysis of granules was measured by using Retsch AS 200 Sieve Shaker. The entire sieve was weighed in descending order. Previously weighed granules were put in sieve shaker. Start the sieve shaker for 5 min at 0.5 mm/g amplitude. Again the entire sieve was weighed in previous manner and calculated the cumulative percentage retained.

Table4: Sieve of analysis SNFML granules: Total amount of drug: 25 gm

SIEVE NO.(µm)	AMOUNT(gm)		PERCENTAGE		CUMULATIVE	
# 40 retains	8.0	5	32	20	32	20
# 60 retains	4.5	7	18	28	50	48
# 80 retains	3.5	5.5	14	22	64	70
# 80 passed	9	7	36	28	100	98

Physical characteristics of bilayered SNFML immediate release Tablets

Table5: Characteristics of bilayered SNFML Tablets

B.No.	Weight variation (mg)	Thickness (mm)	Hardness (N)	Friability (%)
SNFML-1	400 ± 2%	5.3 ± 0.2 mm	140 ± 10 N	0.86
SNFML-2	400 ± 2%	5.3 ± 0.2 mm	140 ± 10 N	0.21
SNFML-3	615 ± 2%	5.5 ± 0.2 mm	150 ± 10 N	0.23
SNFML-4	615 ± 2%	5.5 ± 0.2 mm	150 ± 10 N	0.34
SNFML-5	615 ± 2%	5.5 ± 0.2 mm	150 ± 10 N	0.00
SNFML-6	615 ± 2%	5.5 ± 0.2 mm	150 ± 10 N	0.00
SNFML-7	615 ± 2%	5.5 ± 0.2 mm	150 ± 10 N	0.00
SNFML-8	615 ± 2%	5.5 ± 0.2 mm	150 ± 10 N	0.00

In vitro SNFML release

Table5 Comparative Dissolution values of marketed SNF and Trial 2nd in 0.001 N HCL

Time (min)	% Cumulative drug release	
	Marketed SNF	SNFML-2
10	39.16	42.8
15	57.66	60.3
30	80.33	80
45	92	92
60	97.33	95.2
	F2 value	80.59519

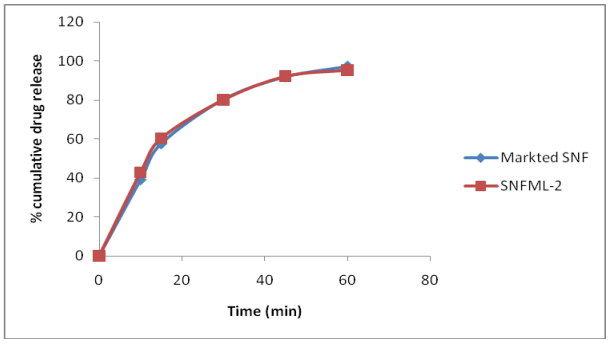

Fig.1: Comparative Dissolution values of marketed SNF and SNFML-2 in 0.001 N HCL

Table6: Comparative Dissolution values of marketed SNML and SNFML-8 in P.w+ 0.5% SLS

Time (min)	% Cumulative drug release	
	Marketed SNML	SNFML-8
10	24.0	20.3
15	43.9	38.0
30	69.7	73.0
45	85.5	88.33
60	94.1	90.5
	F2 value	69.9106

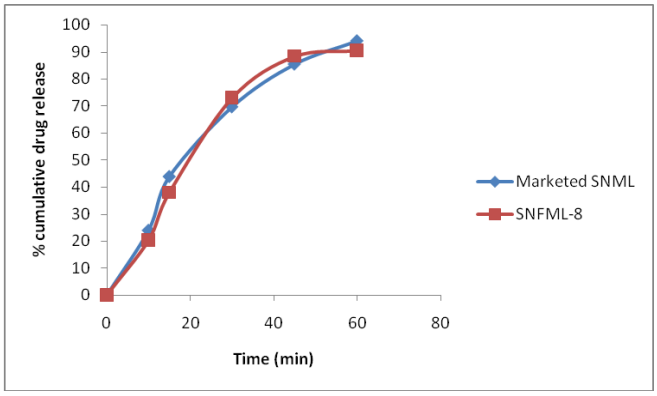

Fig.2: Comparative Dissolution values of marketed SNML and SNFML-8 in P.w+ 0.5% SLS

Table7: Comparative Dissolution profile of SNFML-2 and SNFML-8 with Marketed preparations.

Time (min)	Dissolution medium			
	0.001N HCL		P.w+ 0.5% SLS	
	SNFML-2	Marketed SNF	SNFML-8	Marketed SNML
	% Cumulative drug release			
0	0	0	0	0
10	42.8	39.16	20.3	24.0
15	60.3	57.66	38.0	43.9
30	80	80.33	73.0	69.7
45	92	92	88.33	85.5
60	95.2	97.33	90.5	94.1

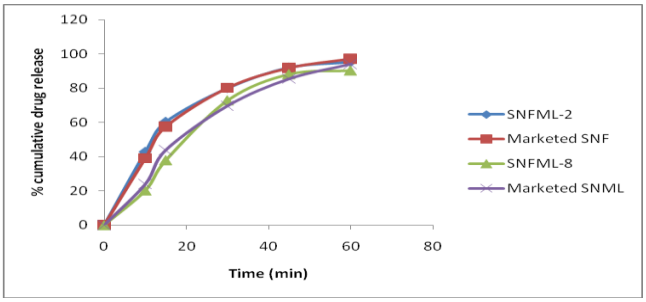

Fig.3: Dissolution profile of SNFML-2 and SNFML-8 with Marketed preparations

DISCUSSION

The solubility of SNML (table 1) was determined in aqueous solvent and buffer solution. The drug was poorly soluble in water. The solubility increases with the addition of SLS.

Based on the preformulation data, eight different batches were developed by using selected excipients. Eight different formulations were present in table 2.

SNFML 1 to 2 were used to develop only for SNF.

In SNFML 1, slow dissolution was observed.

In SNFML 2, Dissolution of this batch was carried out in buffer 0.001 N HCL and F2 value was found 80.59. So it was selected as optimized batch by comparing with marketed preparations.

Comparative dissolution profile of SNFML-2 and marketed products are presented in table. 5 and fig.1.

SNFML-3 to 8 was taken to develop SNML formulations as a bilayered tablet. Dissolution profile of SNFML- 8 batch was present table no.6.

In SNFML-3, flow property of SNML was very poor. This may be due to direct compression method.

SNFML-4, 5, 6, 7 and 8 were prepared by altering the polymer concentrations by wet granulation method. For all batches, dissolution profile was found with marketed preparations and F2 values were below 50% except for SNFML-8.

F2 value of SNFML-8 was found 69.91. Dissolution of this batch was carried out in P.w + 0.5% SLS and comparing with marketed preparations. Dissolution of this batch is presented in table.6 and in fig. 2.

Based on the above results, SNFML-8 was the best formulation.

The similarity factor between SNFML-8 and marketed preparations found to be 81 SNF and 69 SNML (FDA limit 50 to 100) which shows that there is a virtually no differences in release rate from reference formulations and thus the formulation SNFML-8 was selected best formulation.

CONCLUSION

The study was undertaken with an aim to formulate bilayered tablets using drugs SNF and SNML. The literature review showed that these two drugs used for treating allergic condition and their side effects have different mechanism of actions and different pharmacokinetic profiles.

As there were no marketed bilayered tablet of the same combination. Dissolution profile was compared with the SNF innovator and SNML innovator tablets.

Based on dissolution tests, it was concluded that SNFML- 8 satisfactorily performs in the same manners as that of marketed formulation. Dissolution of this batch was carried out in three different pH Medias and compared with marketed preparations. Bilayered tablet preparation using formula listed for SNFML-8(co-sifting of drug) with excipients and use of purified water as binder showed optimum characteristics features.

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REFERENCES

1. Leon Lachmann, Herbert A. Liberman, Joseph L.Kaing, 2008. *The theory and practice of Industrial Pharmacy*, New Jersey, Prentice Hall.
2. Ansel's, 2006. *Pharmaceutical dosage forms & drug delivery systems*, New Jersey, Prentice Hall.
3. Aulton's Pharmaceutics, 2004. *The design & manufacture of medicines, Biopharmaceutics and pharmacokinetics*, *A Treatise*, Valabh Prakashan.
4. Margret C. R., Jayakar.B, Pasupathi, A. Chakrabarty, B.L.Maruya P, 2009. Design, Development and evaluation of immediate release atorvastatin and sustained release gliclazide tablets. *Journal of Pharmacy Research*. Vol 2, Issue 6, pp. 67-72.
5. Chuan-Yu Wu, Jonathan P.K. Seville, 2008. A comparative study of compaction properties of binary and bilayer tablets. *Powder Technology.* Vol.5, Issue 1, pp.285–294.
6. Shiyani B., Dholakiyal R, Akbari B., D.J. Lodhiyal, G.K. Ramani, 2009. Development and evaluation of novel immediate release tablets of Metoclopramide HCL by direct compression using treated gellan gum as disintegration-accelerating agent. *Journal of Pharmacy Research*, Vol. 4, Issue 2, pp. 1460-1464.
7. Huijun Xie, Yong Gan, Suwei Ma, Li Gan and Qinghua Chen, 2009. Optimization and Evaluation of Time-Dependent Tablets Comprising an Immediate and Sustained Release Profile Using Artificial Neural Network. *Drug Development and Industrial Pharmacy*, Vol. 34, Issue 4, pp. 363-372.
8. Guidance for Industry, 1995. Immediate Release Solid Oral Dosage Forms Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, Center for Drug Evaluation and Research (CDER).
9. Guidance for Industry, 1997. Dissolution Testing of Immediate Release Solid Oral Dosage Forms, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).
10. 10. Markus. Vogt, Klaus. Kunath, Jennifer B. Dressman, 2008. Dissolution enhancement of fenofibrate by micronization, co-grinding and spray-drying: Comparison with commercial preparations, *European Journal of Pharmaceutics and Biopharmaceutics,* Vol. 68, pp. 283–288.
11. Guidance for Industry, Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate- Release Solid Oral Dosage Form based on a Biopharmaceutics Classification System. http//www.fda.gov/cder/guidance/index.htm
12. Jonathan Goole, David J. Lindley, Wyatt Roth, Stephen M. Carl, Karim Amighi, Jean-Michel Kauffmann, Gregory T. Knipp, 2010. The effects of excipients on transporter mediated absorption. *International Journal of Pharmaceutics*, Vol 37, Issue 14, pp. 17–31.
13. Vinayak D. Kadam, Surendra G.Gattani, 2009, Dissolution Enhancement Of Carvedilol By Using Surfactant As A Coating Material. *Asian Journal Of Pharmaceutical And Clinical Research*, Vol.2 Issue 3, 39-43.
14. NL Prasanthi, N Rama Rao, SS Manikiran,2010,Studies On Dis solution Enhancement Of Poorly
Water Soluble Drug Using Water Soluble Carriers. *Asian Journal Of Pharmaceutical And Clinical Research*, Vol.3 Issue 2, 95-97.